STIC Search Report
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STIC Database Tracking Number: 145397

TO:	From:
Jennifer Kim Location: 4b02 / 4b18 Thursday, February 17, 2005 Art Unit: 1617 Phone: 272-0628 Serial Number: 10 / 051320	Jan Delaval Location: Biotech-Chem Library Rem 1a51 Phone: 272-2504 jan.delaval@uspto.gov

Search Notes

Jan Delval

Access DB# 145391

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name Jennifer Kim Examiner #: 72469 Date: 2/16/04
Art Unit 1617 Phone Number 30620628 Serial Number: 10/051320
Mail Box and Bldg Room Location Rem 4B02 Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need.

****

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc. if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: Methods to treat autoimmune + inflammatory conditions

Inventors (please provide full names): Shepard

Earliest Priority Filing Date: 1/19/2001

For Sequence Searches Only Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.

1) Please search claims 1 + 20

2) Please display registry # of ~~exact~~ hit cpd claims 1 + 20.

THX,

jlk

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Searcher: lm
Searcher Phone #: 22504
Searcher Location:
Date Searcher Picked Up: 2/17/05
Date Completed: 2/17/05
Searcher Prep & Review Time:
Clerical Prep Time: 10
Online Time: 10

Type of Search
NA Sequence (#)
AA Sequence (#)
Structure (#): ✓
Bibliographic
Litigation
Fulltext
Patent Family
Other

Vendors and cost where applicable
STN: ✓
Dialog
Questel/Orbit
Lexis/Nexis
Sequence Systems
WWW/Internet
Other (specify)

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STRUCTURE FILE UPDATES:   15 FEB 2005  HIGHEST RN 831913-30-5
DICTIONARY FILE UPDATES:  15 FEB 2005  HIGHEST RN 831913-30-5

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 18, 2005

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Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=> d ide can tot l2

L2   ANSWER 1 OF 3  REGISTRY  COPYRIGHT 2005 ACS on STN
RN   474317-98-1  REGISTRY
CN   Alanine, N-[5-(2-bromoethenyl)-2'-deoxy-P-phenyl-5'-uridylyl]-, methyl
     ester (9CI)  (CA INDEX NAME)
FS   STEREOSEARCH
MF   C21 H25 Br N3 O9 P
SR   CA
LC   STN Files:   CA, CAPLUS, TOXCENTER, USPATFULL
DT.CA  CAplus document type:  Patent
RL.P   Roles from patents:  BIOL (Biological study); USES (Uses)

Absolute stereochemistry.
Double bond geometry unknown.
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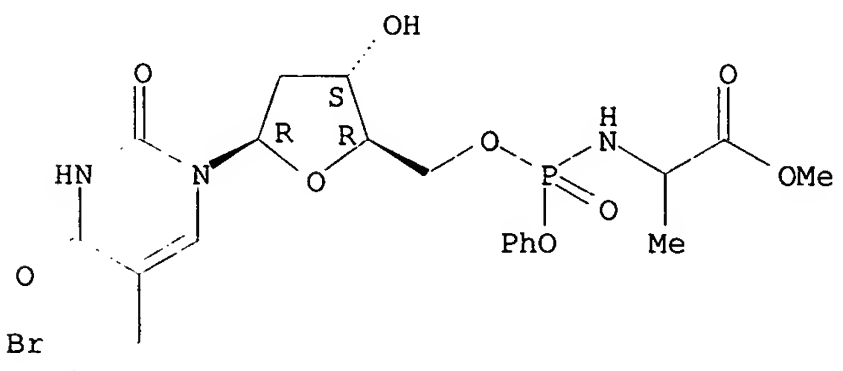


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**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

               1 REFERENCES IN FILE CA (1907 TO DATE)
               1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE   1:  137:375228

L2   ANSWER 2 OF 3  REGISTRY  COPYRIGHT 2005 ACS on STN
RN   322454-65-9  REGISTRY
CN   L-Alanine, N-[5-(2-bromoethenyl)-2'-deoxy-P-phenyl-5'-uridylyl]-, methyl
     ester (9CI)  (CA INDEX NAME)
FS   STEREOSEARCH
MF   C21 H25 Br N3 O9 P
SR   CA
LC   STN Files:   CA, CAPLUS, TOXCENTER, USPATFULL
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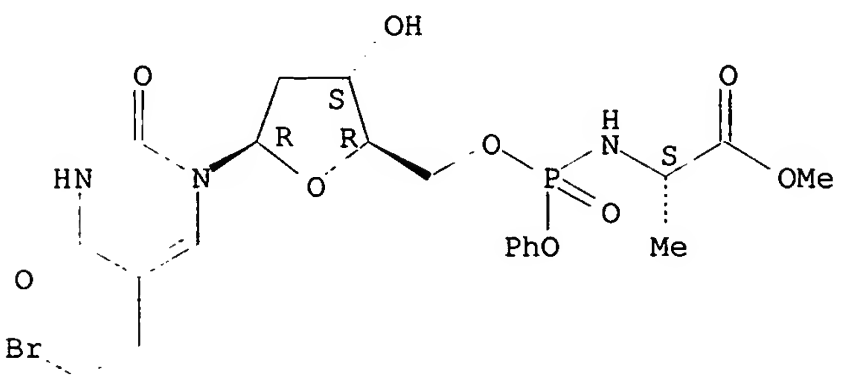
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)

Absolute stereochemistry.
Double bond geometry unknown.



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4 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 139:7127

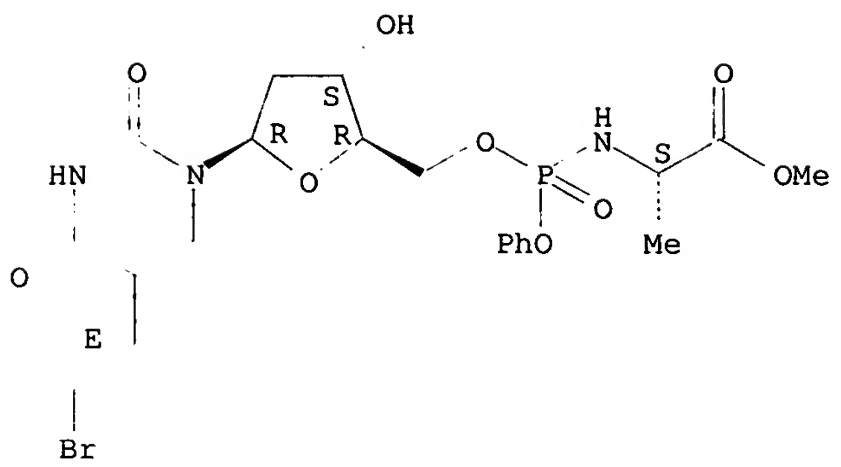
REFERENCE 2: 137:103888

REFERENCE 3: 136:386347

REFERENCE 4: 134:141727

L2 ANSWER 3 OF 3 REGISTRY COPYRIGHT 2005 ACS on STN
RN 232925-18-7 REGISTRY
CN L-Alanine, N-[5-[(1E)-2-bromoethenyl]-2'-deoxy-P-phenyl-5'-uridylyl]-, methyl ester (9CI) (CA INDEX NAME)
OTHER NAMES:
CN NB 1011
FS STEREOSEARCH
MF **C21 H25 Br N3 O9 P**
SR CA
LC STN Files: BIOSIS, CA, CAPLUS, CASREACT, IMSDRUGNEWS, IMSRESEARCH, PROUSDDR, RTECS*, SYNTHLINE, TOXCENTER, USPATFULL
(*File contains numerically searchable property data)
DT.CA CAplus document type: Journal; Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
RL.NP Roles from non-patents: BIOL (Biological study); PREP (Preparation); PRP (Properties); RACT (Reactant or reagent); USES (Uses)
RLD.NP Roles for non-specific derivatives from non-patents: BIOL (Biological study); PREP (Preparation); USES (Uses)

Absolute stereochemistry.
Double bond geometry as shown.



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14 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 140:64854

REFERENCE 2: 140:35438

REFERENCE 3: 140:35079

REFERENCE 4: 139:316719

REFERENCE 5: 139:242183

REFERENCE 6: 139:190589

REFERENCE 7: 138:248065

REFERENCE 8: 137:295185

REFERENCE 9: 137:272912

REFERENCE 10: 137:210903

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L1 11977 S 46.150.18/RID AND (OC4 AND NCNC3)/ES AND 3/NR
L2 3 S L1 AND C21H25BRN3O9P

FILE 'HCAOLD' ENTERED AT 10:13:51 ON 17 FEB 2005
L3 0 S L2

FILE 'HCAPLUS' ENTERED AT 10:13:53 ON 17 FEB 2005
L4 19 S L2
L5 10 S NB1011 OR NB 1011
L6 19 S L4,L5
L7 9 S L6 AND SHEPARD ?/AU
L8 13 S L6 AND NEWBIOT?/PA,CS
L9 8 S L6 AND (PD<=20010119 OR PRD<=20010119 OR AD<=20010119)
L10 7 S L7,L8 AND L9
L11 8 S L9,L10
L12 11 S L6-L10 NOT L11

FILE 'USPATFULL' ENTERED AT 10:16:03 ON 17 FEB 2005
L13 11 S L2

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L14           8 S L5
L15          13 S L13,L14
L16          10 S L15 AND (PD<=20010119 OR PRD<=20010119 OR AD<=20010119)

     FILE 'BIOSIS' ENTERED AT 10:16:52 ON 17 FEB 2005
L17          13 S L2 OR L5
L18           7 S L17 AND PY<=2001

     FILE 'EMBASE' ENTERED AT 10:17:20 ON 17 FEB 2005
L19           0 S L2
L20          11 S L5
L21           1 S 5 2 BROMOVINYL 2 DEOXY 5 URIDYLPHENYLALANYLPHOSPHORAMIDATE
L22          11 S L20,L21
L23           3 S L22 AND PY<=2001

     FILE 'HCAPLUS, BIOSIS, EMBASE' ENTERED AT 10:19:38 ON 17 FEB 2005
L24          14 DUP REM L11 L18 L23 (4 DUPLICATES REMOVED)

     FILE 'REGISTRY' ENTERED AT 10:20:03 ON 17 FEB 2005

=> fil hcaplus biosis embase
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=> d l24 all hitstr tot
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L24 ANSWER 1 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 1
AN 2001:167005 HCAPLUS
DN 134:361084
ED Entered STN: 09 Mar 2001
TI A novel approach to thymidylate synthase as a target for cancer chemotherapy
AU Li, Qing; Boyer, Christopher; Lee, Jean Y.; **Shepard, H. Michael**
CS **NewBiotics, Inc., San Diego, CA, USA**
SO Molecular Pharmacology (**2001**), 59(3), 446-452
CODEN: MOPMA3; ISSN: 0026-895X
PB American Society for Pharmacology and Experimental Therapeutics
DT Journal
LA English
CC 1-6 (Pharmacology)
AB Tumor cell resistance to fluoropyrimidiness and other inhibitors of thymidylate synthase (TS) is a serious problem often associated with increased intracellular TS. Clin., another problem that arises from the use of TS inhibitors is toxicity, which develops, in part, because normal cells may be adversely affected by doses of inhibitor that do not impact tumor cells. To circumvent this problem, we have devised a new strategy called enzyme-catalyzed therapeutic activation (ECTA), which takes advantage of overexpressed TS to enzymically generate cytotoxic moieties preferentially in tumor cells. We show herein that tumor cells expressing elevated levels of TS are preferentially sensitive to **NB1011**, a phosphoramidate derivative of (E)-5-(2-bromovinyl)-2'-deoxyuridine. We find support for the proposed mechanism of **NB1011** in the following results: (1) pos. relationship between TS protein level and sensitivity to **NB1011** in engineered HT1080 tumor cells, designed to express defined levels of TS protein; (2) **NB1011** activity is enhanced on tumor cells which express endogenous elevated TS; (3) cytotoxicity of **NB1011** is blocked by raltitrexed (Tomudex); (4) **NB1011** selection of TS-overexpressing MCF7TDX tumor cells results in recovery of cell populations and clones with diminished TS levels and restored sensitivity to raltitrexed. A preliminary comparison of TS mRNA levels in multiple normal tissues vs. colon tumor samples suggests that selective

tumor cytotoxicity of **NB1011** may be possible in the clin. setting. Because **NB1011** cytotoxicity is dependent upon activation by TS, its proposed mechanism of action is distinct from current TS-targeted drugs, which require inhibition of TS to be effective.

ST thymidylate synthase **NB1011** antitumor colon tumor

IT Drug resistance
(antitumor; a novel approach to thymidylate synthase as a target for cancer chemotherapy)

IT Intestine, neoplasm
(colon, inhibitors; a novel approach to thymidylate synthase as a target for cancer chemotherapy)

IT Antitumor agents
(colon; a novel approach to thymidylate synthase as a target for cancer chemotherapy)

IT Antitumor agents
(mammary gland; a novel approach to thymidylate synthase as a target for cancer chemotherapy)

IT Mammary gland
(neoplasm, inhibitors; a novel approach to thymidylate synthase as a target for cancer chemotherapy)

IT Antitumor agents
(resistance to; a novel approach to thymidylate synthase as a target for cancer chemotherapy)

IT **232925-18-7, NB1011**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(a novel approach to thymidylate synthase as a target for cancer chemotherapy)

IT 9031-61-2, Thymidylate synthase
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(a novel approach to thymidylate synthase as a target for cancer chemotherapy)

RE.CNT 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

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(2) Almasan, A; Proc Natl Acad Sci USA 1995, V92, P5436 HCAPLUS
(3) Balzarini, J; Mol Pharmacol 1987, V32, P410 HCAPLUS
(4) Bannerjee, D; Cancer Res 1998, V58, P4292
(5) Barr, P; J Biol Chem 1983, V258, P13627 HCAPLUS
(6) Bathe, O; Cancer J Sci Am 1999, V5, P34 MEDLINE
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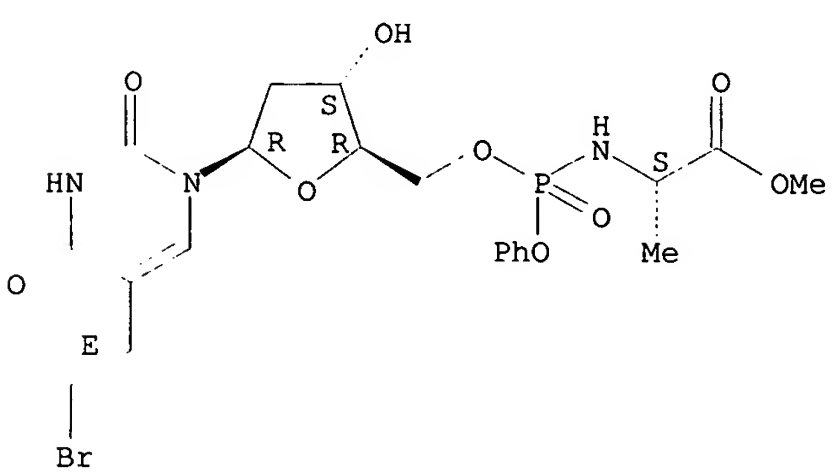
(37) Sugarman, B; Science 1985, V230, P943 HCAPLUS
(38) Wahl, G; Cancer Surv 1997, V29, P183 HCAPLUS

IT **232925-18-7, NB1011**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(a novel approach to thymidylate synthase as a target for cancer chemotherapy)

RN 232925-18-7 HCAPLUS

CN L-Alanine, N-[5-[(1E)-2-bromoethenyl]-2'-deoxy-P-phenyl-5'-uridylyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L24 ANSWER 2 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 2
AN 2001:24117 HCAPLUS
DN 134:290064
ED Entered STN: 10 Jan 2001
TI Enzyme-catalyzed therapeutic agent (ECTA) design: activation of the antitumor ECTA compound **NB1011** by thymidylate synthase
AU Lackey, D. B.; Groziak, M. P.; Sergeeva, M.; Beryt, M.; Boyer, C.; Stroud, R. M.; Sayre, P.; Park, J. W.; Johnston, P.; Slamon, D.; **Shepard, H. M.**; Pegram, M.
CS **NewBiotics, Inc., San Diego, CA, 92121, USA**
SO Biochemical Pharmacology (**2001**), 61(2), 179-189
CODEN: BCPCA6; ISSN: 0006-2952
PB Elsevier Science Inc.
DT Journal
LA English
CC 1-6 (Pharmacology)
AB The in vivo administration of enzyme-inhibiting drugs for cancer and infectious disease often results in overexpression of the targeted enzyme. We have developed an enzyme-catalyzed therapeutic agent (ECTA) approach in which an enzyme overexpressed within the resistant cells is recruited as an intracellular catalyst for converting a relatively non-toxic substrate to a toxic product. We have investigated the potential of the ECTA approach to circumvent the thymidylate synthase (TS) overexpression-based resistance of tumor cells to conventional fluoropyrimidine [i.e. 5-fluorouracil (5-FU)] cancer chemotherapy. (E)-5-(2-Bromovinyl)-2'-deoxy-5'-uridyl Ph 1-methoxyalaninylphosphoramidate (**NB1011**) is a pronucleotide analog of (E)-5-(2-bromovinyl)-2'-deoxyuridine (BVdU), an antiviral agent known to be a substrate for TS when in the 5'-monophosphorylated form. **NB1011** was synthesized and found to be at least 10-fold more cytotoxic to 5-FU-resistant, TS-overexpressing colorectal tumor cells than to normal cells. This finding demonstrates that the ECTA approach to the design of novel chemotherapeutics results in compds. that are selectively cytotoxic to tumor cell lines that overexpress the target enzyme, TS, and therefore may be useful in the treatment of fluoropyrimidine-resistant cancer.

ST antitumor **NB1011** thymidylate synthase catalyzed
IT Drug resistance
(antitumor; enzyme-catalyzed therapeutic agent design: activation of antitumor **NB1011** by thymidylate synthase)
IT Intestine, neoplasm
(colorectal, inhibitors; enzyme-catalyzed therapeutic agent design: activation of antitumor **NB1011** by thymidylate synthase)
IT Antitumor agents
(colorectal; enzyme-catalyzed therapeutic agent design: activation of antitumor **NB1011** by thymidylate synthase)
IT 9031-61-2, Thymidylate synthase
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(enzyme-catalyzed therapeutic agent design: activation of antitumor **NB1011** by thymidylate synthase)
IT 51-21-8, 5-Fluorouracil **232925-18-7, NB 1011**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(enzyme-catalyzed therapeutic agent design: activation of antitumor **NB1011** by thymidylate synthase)
IT 80860-82-8 334869-75-9 334869-76-0 334869-77-1
RL: BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(enzyme-catalyzed therapeutic agent design: activation of antitumor **NB1011** by thymidylate synthase)
IT 69304-47-8, BVdU 142629-80-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(enzyme-catalyzed therapeutic agent design: activation of antitumor **NB1011** by thymidylate synthase)
RE.CNT 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Almasan, A; Cancer Metastasis Rev 1995, V14, P59 HCAPLUS
(2) Balzarini, J; J Acquir Immune Defic Syndr Hum Retrovirol 1998, V17, P296 HCAPLUS
(3) Barr, P; J Biol Chem 1983, V258, P13627 HCAPLUS
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(14) Levasseur, L; Cancer Res 1998, V58, P5749 HCAPLUS
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(21) Peters, G; Eur J Cancer 1995, V31A, P1299 HCAPLUS
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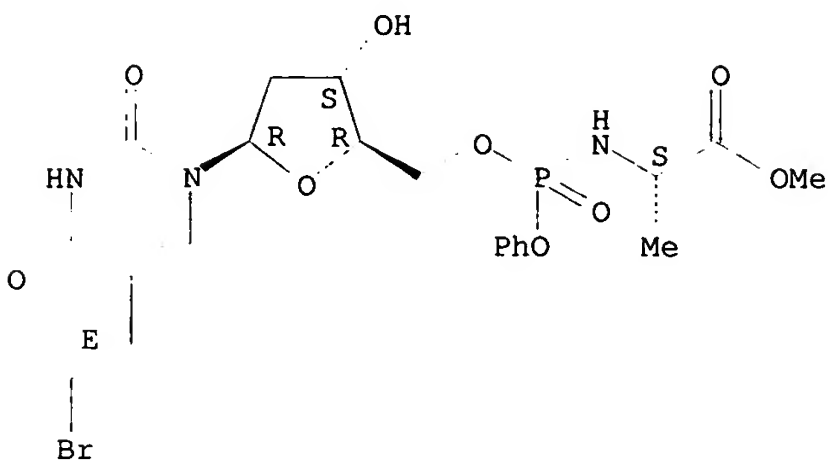
(23) Saboulard, D; Mol Pharmacol 1999, V56, P693 HCAPLUS
(24) Schiffer, C; Biochemistry 1995, V34, P16279 HCAPLUS
IT **232925-18-7, NB 1011**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(enzyme-catalyzed therapeutic agent design: activation of antitumor **NB1011** by thymidylate synthase)
RN 232925-18-7 HCAPLUS
CN L-Alanine, N-[5-[(1E)-2-bromoethenyl]-2'-deoxy-P-phenyl-5'-uridylyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

Double bond geometry as shown.



L24 ANSWER 3 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2003:455061 HCAPLUS
DN 139:7127
ED Entered STN: 13 Jun 2003
TI Preparation, cytotoxicity, antitumor, and antiinflammatory activities of nucleoside phosphoramidates
IN **Shepard, H. Michael**; Vaino, Andrew Rein; Lehsten, Danielle M.
PA USA
SO U.S. Pat. Appl. Publ., 58 pp., Cont.-in-part of U.S. Ser. No. 782,721.
CODEN: USXXCO
DT Patent
LA English
IC ICM C07H019-048
ICS C07H019-10; A61K031-7072
NCL 536026800; 514051000
CC 33-9 (Carbohydrates)
Section cross-reference(s): 1, 7, 63
FAN.CNT 2

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	EP 1167972	A2	20020102	EP 2001-120242	19990122 <--
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	US 6339151	B1	20020115	US 1999-235961	19990122 <--
	JP 2001220397	A2	20010814	JP 2000-339831	20001108 <--
	JP 3265304	B2	20020311		
	US 2001034440	A1	20011025	US 2001-782721	20010212 <--
PRAI	US 1998-72264P	P	19980123 <--		
	US 1998-76950P	P	19980305 <--		
	US 1998-108634P	P	19981116 <--		
	US 1999-235961	A1	19990122 <--		
	US 2001-782721	A2	20010212		
	EP 1999-904195	A3	19990122 <--		
	JP 2000-528661	A3	19990122 <--		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
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	NCL	536026800; 514051000
EP 1167972	ECLA	A61K047/48H4 <--
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OS MARPAT 139:7127
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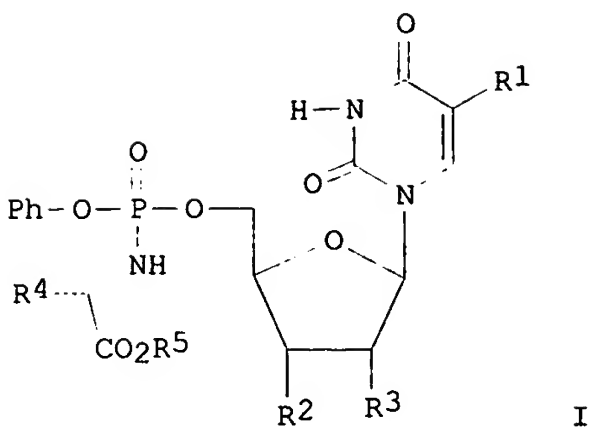


I

AB This invention provides compds., compns. and methods for treating cancer, infectious disease, an autoimmune disorder or an inflammatory condition. Therapeutic compds. useful in the methods of this invention are 5'-phosphoramidatyl, 1,5-substituted pyrimidine compds. I, wherein and pharmaceutically acceptable salts thereof. Thus, I (R1 = CH:CHBr, R2 = OH, R3 = H, R4 = Me, R5 = Et) was prepared and tested for its cytotoxicity, antitumor, and antiinflammatory activities. Expression of thymidylate synthase in human normal tissues. The thymidylate synthase (TS) expression level in normal human tissues was examined in order to estimate the systemic toxicity of the compound(s) activated by thymidylate synthase.

ST thymidylate synthase human cytotoxicity antitumor antiinflammatory prepn nucleotide; human cytotoxicity antitumor antiinflammatory prepn nucleoside phosphoramidate nucleotide

IT Anemia (disease)
Autoimmune disease
(autoimmune hemolytic anemia; preparation cytotoxicity antitumor and antiinflammatory activities of nucleoside phosphoramidates)

IT Anti-inflammatory agents
Antiarthritics
Antitumor agents
Arthritis
Autoimmune disease
Cytotoxic agents
Cytotoxicity
Drugs
Human
Inflammation
Neoplasm
Rheumatoid arthritis
(preparation cytotoxicity antitumor and antiinflammatory activities of nucleoside phosphoramidates)

IT Nucleosides, preparation
Nucleotides, preparation
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation cytotoxicity antitumor and antiinflammatory activities of nucleoside phosphoramidates)

IT 9031-61-2, Thymidylate synthase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(human; preparation cytotoxicity antitumor and antiinflammatory activities of nucleoside phosphoramidates)

IT 142629-80-9P 321982-16-5P 321982-20-1P 321982-22-3P 321982-24-5P
321982-26-7P 321982-28-9P 321982-30-3P 321982-34-7P 322454-13-7P
322454-48-8P **322454-65-9P** 436097-54-0P 535958-45-3P
535958-46-4P 535958-47-5P 535958-48-6P 535958-49-7P 535958-50-0P
535958-51-1P 535958-52-2P 535958-53-3P 535958-54-4P 535958-55-5P
535958-57-7P 535958-58-8P 535958-59-9P 535958-60-2P 535958-61-3P
535958-62-4P 535958-63-5P 535958-64-6P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation cytotoxicity antitumor and antiinflammatory activities of nucleoside phosphoramidates)

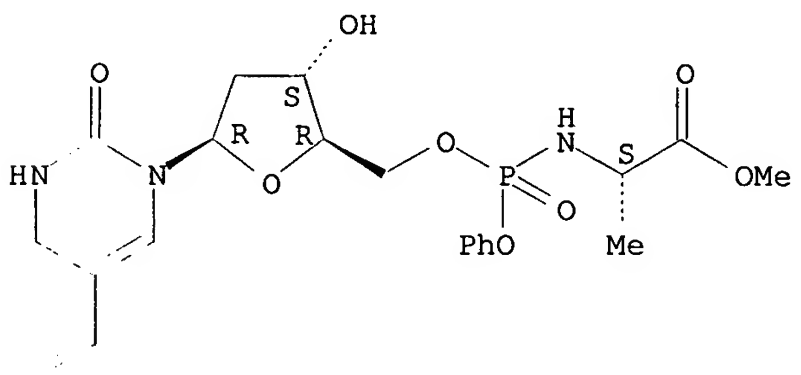
IT 54-42-2 100-02-7, p-Nitrophenol, reactions 110-87-2 128-08-5, N-Bromosuccinimide 77875-99-1 96244-97-2
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation cytotoxicity antitumor and antiinflammatory activities of nucleoside phosphoramidates)

IT 157085-09-1P 322454-46-6P 322454-51-3P 322454-53-5P 322454-55-7P 322454-59-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation cytotoxicity antitumor and antiinflammatory activities of nucleoside phosphoramidates)

IT **322454-65-9P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation cytotoxicity antitumor and antiinflammatory activities of nucleoside phosphoramidates)

RN 322454-65-9 HCAPLUS
CN L-Alanine, N-[5-(2-bromoethenyl)-2'-deoxy-P-phenyl-5'-uridylyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



L24 ANSWER 4 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2002:555307 HCAPLUS
DN 137:103888
ED Entered STN: 26 Jul 2002
TI Methods using pyrimidine derivatives and furanopyrimidone derivatives to treat autoimmune and inflammatory conditions
IN **Shepard, H. Michael**
PA **Newbiotics, Inc., USA**
SO PCT Int. Appl., 65 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K
CC 1-7 (Pharmacology)
Section cross-reference(s): 33
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2002056832	A2	20020725	WO 2002-US1361	20020118 <--
WO 2002056832	A3	20030306		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,

BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
CA 2441350 AA 20020725 CA 2002-2441350 20020118 <--
US 2002151519 A1 20021017 US 2002-51320 20020118 <--
EP 1359921 A2 20031112 EP 2002-707508 20020118 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
PRAI US 2001-262849P P 20010119 <--
WO 2002-US1361 W 20020118

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2002056832	ICM	A61K
US 2002151519	ECLA	A61K031/513; A61K031/519; A61K031/675; A61K031/7068; A61K031/7072 <--

AB The invention provides methods for treating inflammatory or autoimmune diseases by contacting the affected cell or tissue with a therapeutic compound Such pathologies include, but are not limited to, rheumatoid arthritis, systemic lupus erythematosus, psoriatic arthritis, reactive arthritis, Crohn's disease, ulcerative colitis, and scleroderma. Therapeutic compds. useful in the methods of this invention are selected from 1,5-substituted pyrimidine derivs. and analogs and substituted furanopyrimidone analogs. Compound preparation is included.

.ST pyrimidine deriv furanopyrimidone deriv autoimmune inflammatory disease therapeutic

IT Inflammation
(Crohn's disease; pyrimidine derivs. and furanopyrimidone derivs.,for treatment of autoimmune and inflammatory conditions)

IT Intestine, disease
(Crohn's; pyrimidine derivs. and furanopyrimidone derivs.,for treatment of autoimmune and inflammatory conditions)

IT Tumor necrosis factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(anti-TNF agents; pyrimidine derivs. and furanopyrimidone derivs.,for treatment of autoimmune and inflammatory conditions, and use with other agents)

IT Antibodies and Immunoglobulins
RL: PAC (Pharmacological activity); BIOL (Biological study)
(anti-TNF; pyrimidine derivs. and furanopyrimidone derivs.,for treatment of autoimmune and inflammatory conditions)

IT Antiarteriosclerotics
(antiatherosclerotics; pyrimidine derivs. and furanopyrimidone derivs.,for treatment of autoimmune and inflammatory conditions)

IT Drugs
(gastrointestinal; pyrimidine derivs. and furanopyrimidone derivs.,for treatment of autoimmune and inflammatory conditions)

IT Inflammation
Kidney, disease
(glomerulonephritis; pyrimidine derivs. and furanopyrimidone derivs.,for treatment of autoimmune and inflammatory conditions)

IT Transplant and Transplantation
(graft-vs.-host reaction; pyrimidine derivs. and furanopyrimidone derivs.,for treatment of autoimmune and inflammatory conditions)

IT Intestine, disease
(inflammatory; pyrimidine derivs. and furanopyrimidone derivs.,for treatment of autoimmune and inflammatory conditions)

IT Diabetes mellitus
(insulin-dependent; pyrimidine derivs. and furanopyrimidone derivs.,for treatment of autoimmune and inflammatory conditions)

IT Anti-inflammatory agents
(nonsteroidal; pyrimidine derivs. and furanopyrimidone derivs.,for treatment of autoimmune and inflammatory conditions, and use with other agents)

IT Arthritis
(psoriatic arthritis; pyrimidine derivs. and furanopyrimidone derivs.,for treatment of autoimmune and inflammatory conditions)

IT Anti-inflammatory agents
Antiarthritics
Antiasthmatics
Antidiabetic agents

Arthritis
Asthma
Atherosclerosis
Autoimmune disease
Drug screening
Inflammation
Multiple sclerosis
Muscular dystrophy
Myasthenia gravis
Osteoarthritis
Psoriasis
Rheumatoid arthritis
Sjogren's syndrome
(pyrimidine derivs. and furanopyrimidone derivs.,for treatment of autoimmune and inflammatory conditions)

IT Antirheumatic agents
(pyrimidine derivs. and furanopyrimidone derivs.,for treatment of autoimmune and inflammatory conditions, and use with other agents)

IT Corticosteroids, biological studies
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pyrimidine derivs. and furanopyrimidone derivs.,for treatment of autoimmune and inflammatory conditions, and use with other agents)

IT Arthritis
(reactive; pyrimidine derivs. and furanopyrimidone derivs.,for treatment of autoimmune and inflammatory conditions)

IT Connective tissue, disease
(scleroderma; pyrimidine derivs. and furanopyrimidone derivs.,for treatment of autoimmune and inflammatory conditions)

IT Lupus erythematosus
(systemic; pyrimidine derivs. and furanopyrimidone derivs.,for treatment of autoimmune and inflammatory conditions)

IT Multiple sclerosis
(therapeutic agents; pyrimidine derivs. and furanopyrimidone derivs.,for treatment of autoimmune and inflammatory conditions)

IT Inflammation
Intestine, disease
(ulcerative colitis; pyrimidine derivs. and furanopyrimidone derivs.,for treatment of autoimmune and inflammatory conditions)

IT 142629-80-9P 322454-46-6P 322454-48-8P 322454-51-3P 322454-53-5P 322454-55-7P 322454-59-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction; pyrimidine derivs. and furanopyrimidone derivs.,for treatment of autoimmune and inflammatory conditions)

IT **322454-65-9P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(pyrimidine derivs. and furanopyrimidone derivs.,for treatment of autoimmune and inflammatory conditions)

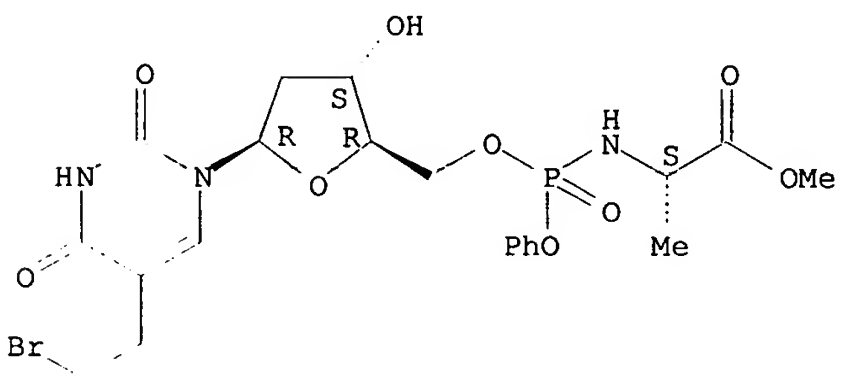
IT 289-95-2D, Pyrimidine, 1,5-substituted derivs. 964-26-1D, derivs. 82768-44-3D, derivs. 321982-16-5
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pyrimidine derivs. and furanopyrimidone derivs.,for treatment of autoimmune and inflammatory conditions)

IT 157085-09-1P 321982-20-1P 321982-22-3P 321982-24-5P 321982-26-7P 321982-28-9P 321982-30-3P 321982-34-7P 322454-13-7P 322454-17-1P
RL: SPN (Synthetic preparation); PREP (Preparation)
(pyrimidine derivs. and furanopyrimidone derivs.,for treatment of autoimmune and inflammatory conditions)

IT 54-42-2, 5-Iodo-2'-deoxyuridine 100-02-7, 4-Nitrophenol, reactions 110-87-2, 3,4-Dihydro-2H-pyran 770-12-7 1099-45-2 1515-75-9, Methyl 2,4-pentadienoate 2491-20-5, L-Alanine methyl ester hydrochloride 77875-99-1 82768-44-3, 5-(2-Bromovinyl)-2'-deoxyuridine 96244-97-2
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction; pyrimidine derivs. and furanopyrimidone derivs.,for treatment of autoimmune and inflammatory conditions)

IT **322454-65-9P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(pyrimidine derivs. and furanopyrimidone derivs.,for treatment of autoimmune and inflammatory conditions)
RN 322454-65-9 HCAPLUS
CN L-Alanine, N-[5-(2-bromoethenyl)-2'-deoxy-P-phenyl-5'-uridylyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



L24 ANSWER 5 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2002:391469 HCAPLUS
DN 136:386347
ED Entered STN: 24 May 2002
TI Preparation of synergistic enzyme catalyzed therapeutic activation (ECTA) nucleosides as antitumor agents
IN **Shepard, H. Michael**; Boyer, Christopher
PA **Newbiotics, Inc., USA**
SO PCT Int. Appl., 72 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K
CC 33-9 (Carbohydrates)
Section cross-reference(s): 1, 7, 34, 63
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002039952	A2	20020523	WO 2001-US43566	20011116 <--
	WO 2002039952	A3	20021010		
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	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	AU 2002036455	A5	20020527	AU 2002-36455	20011116 <--
	US 2002147175	A1	20021010	US 2001-990799	20011116 <--
PRAI	US 2000-249722P	P	20001116 <--		
	WO 2001-US43566	W	20011116		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2002039952	ICM	A61K
US 2002147175	ECLA	A61K047/48H4; A61K047/48R6F <--

AB This invention provides compns. containing an effective amount of a novel substrate compound that selectively inhibit the proliferation of hyper-proliferative cells, for example, pathol. cells that endogenously over-express a target enzyme that confers resistance to biol. and

chemo-therapeutic agents and an effective amount of a nucleoside transport antagonistic agents. Further provided by this invention is a method for treating a subject by delivering to the subject the composition as described herein. The compns. of this invention may be used alone or in combination with other chemo-therapeutics or alternative anti-cancer therapies such as radiation. Thus, (E)-5-(2-bromovinyl)-2'-deoxy-5'-uridyl Ph L-alaninylphosphoramidate (I) was prepared and tested in vitro human cells as synergistic antitumor agent. Vinblastine and doxorubicin showed potential synergy (CI < 1.1) with I in MCF7TDX and H630R10 cell. Irinotecan and taxol showed an additive or antagonistic interaction (CI = 1-1.4). The most antagonistic interaction was observed with 5-fluorouracil which gave CI = 3.19 in MCF7TDX cells. In light of these results, vinblastine and doxorubicin were chosen for further study.

ST alaninyl nucleoside antitumor prepn enzyme catalyzed therapeutic activation glycerolipid; drug interaction synergistic nucleoside antitumor prepn cytotoxicity human; synergistic ECTA nucleoside antitumor prepn enzyme catalyzed therapeutic activation

IT Human
(cells; preparation of synergistic enzyme catalyzed therapeutic activation nucleosides as antitumor agents)

IT Cell proliferation
(inhibition; preparation of synergistic enzyme catalyzed therapeutic activation nucleosides as antitumor agents)

IT Cytotoxic agents
Cytotoxicity
Drug interactions
(preparation of synergistic enzyme catalyzed therapeutic activation nucleosides as antitumor agents)

IT Nucleosides, preparation
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of synergistic enzyme catalyzed therapeutic activation nucleosides as antitumor agents)

IT Antitumor agents
(synergistic; preparation of synergistic enzyme catalyzed therapeutic activation nucleosides as antitumor agents)

IT 51-21-8, 5-Fluorouracil 52-24-4, Thiotepa 58-32-2, Dipyridamole 59-05-2, Methotrexate 60-81-1, Phloridzin 60-82-2, Phloretin 68-94-0, Hypoxanthine 73-24-5, Adenine, biological studies 315-30-0, Allopurinol 865-21-4, Vinblastine 1214-39-7, 6-Benzylaminopurine 3416-26-0, Lidoflazin 6974-78-3, 8-Bromoadenine 9031-61-2, Thymidylate synthase 14930-96-2, Cytochalasin B 15663-27-1, Cisplatin 23214-92-8, Doxorubicin 33069-62-4, Taxol 33419-42-0, Etoposide 35898-87-4, Dilazep 38048-32-7 59277-89-3, (Acyclovir) 61825-94-3, Oxaliplatin 79467-23-5, Mioflazine 82410-32-0, Ganciclovir 85326-06-3, 2',3'-Dideoxyguanosine 97682-44-5, Irinotecan 104889-68-1 123948-87-8, Topotecan
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of synergistic enzyme catalyzed therapeutic activation nucleosides as antitumor agents)

IT 157085-09-1P 321982-16-5P 321982-20-1P 321982-22-3P 321982-24-5P 321982-26-7P 321982-28-9P 321982-30-3P 321982-34-7P 322454-13-7P 322454-17-1P **322454-65-9P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of synergistic enzyme catalyzed therapeutic activation nucleosides as antitumor agents)

IT 54-42-2 100-02-7, 4-Nitrophenol, reactions 1099-45-2, (Carbethoxymethylene)triphenylphosphorane 1515-75-9, Methyl 2,4-pentadienoate 2446-83-5, Diisopropyl azodicarboxylate 2491-20-5, L-Alanine methyl ester hydrochloride 77875-99-1 82768-44-3 96244-97-2
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of synergistic enzyme catalyzed therapeutic activation nucleosides as antitumor agents)

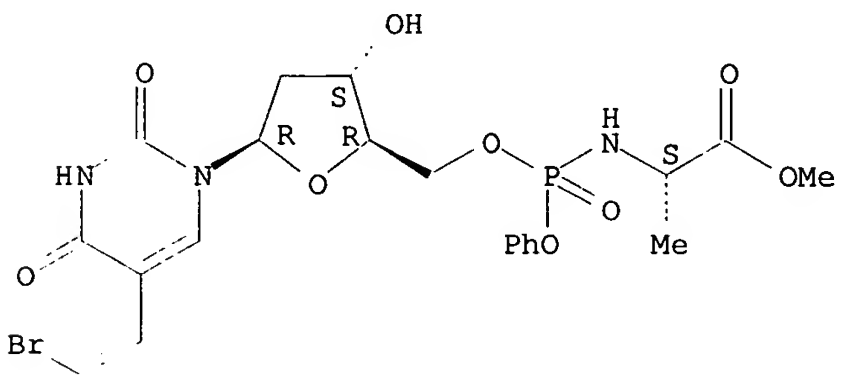
IT 142629-80-9P 322454-46-6P 322454-48-8P 322454-51-3P 322454-53-5P 322454-55-7P 322454-59-1P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of synergistic enzyme catalyzed therapeutic activation nucleosides as antitumor agents)

IT **322454-65-9P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of synergistic enzyme catalyzed therapeutic activation nucleosides as antitumor agents)

RN 322454-65-9 HCAPLUS
CN L-Alanine, N-[5-(2-bromoethenyl)-2'-deoxy-P-phenyl-5'-uridylyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



L24 ANSWER 6 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2001:78399 HCAPLUS
DN 134:141727
ED Entered STN: 02 Feb 2001
TI Enzyme-catalyzed therapeutic activation, tetrahydropyrimidine derivative prodrugs, and preparation and antitumor activity thereof
IN **Shepard, H. Michael**; Chan, Ming Fai; Groziak, Michael P.
PA **Newbiotics, Inc., USA**
SO PCT Int. Appl., 106 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07H019-04
ICS C12N009-10; A61K031-706; A61P035-00
CC 1-6 (Pharmacology)
Section cross-reference(s): 28, 33, 63
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001007454	A1	20010201	WO 2000-US20008	20000721 <--
	W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
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	AU 2000062319	A5	20010213	AU 2000-62319	20000721 <--
	AU 775601	B2	20040805		
	EP 1200455	A1	20020502	EP 2000-948886	20000721 <--
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	JP 2003505466	T2	20030212	JP 2001-512538	20000721 <--
	BR 2000012677	A	20030701	BR 2000-12677	20000721 <--
	US 6683061	B1	20040127	US 2001-856127	20011010 <--

	US 2004077588	A1	20040422	US 2003-681418	20031007 <--
PRAI	US 1999-145356P	P	19990722 <--		
	US 1999-145437P	P	19990723 <--		
	US 2000-191315P	P	20000321 <--		
	WO 2000-US20008	W	20000721 <--		
	US 2001-856127	A1	20011010		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2001007454	ICM	C07H019-04
	ICS	C12N009-10; A61K031-706; A61P035-00

OS MARPAT 134:141727

AB Substrate compds. are provided that selectively inhibit the proliferation of pathol. cells, e.g. pathol. cells that endogenously overexpress a target enzyme that confers resistance to biol. and chemotherapeutic agents. The enzyme acts on a substrate compound to (1) convert it to a cellular toxin and/or (2) release a toxic byproduct. In one embodiment, the activity of the target enzyme has been greatly enhanced in a target cell as a result of loss of tumor suppressor function and/or selection resulting from previous exposure to chemotherapy. In another embodiment, the pathol. cell contains a target enzyme that is an expression product of an infectious agent in the cell. Further provided is a method for treating a subject by delivering to the subject a prodrug as described herein. The prodrugs of the invention may be used alone or in combination with other chemotherapeutics or alternative anti-cancer therapies such as radiation. Preparation of deoxyuridine derivs. is described.

ST tetrahydropyrimidine deriv enzyme activation prodrug antitumor; deoxyuridine deriv prepn enzyme activation prodrug

IT Lymphocyte
(PBL, thymidylate synthase expression in; enzyme-catalyzed therapeutic activation, tetrahydropyrimidine derivative prodrugs, and preparation and antitumor activity)

IT Mammary gland
(adenocarcinoma, inhibitors; enzyme-catalyzed therapeutic activation, tetrahydropyrimidine derivative prodrugs, and preparation and antitumor activity)

IT Mammary gland
(adenocarcinoma, thymidylate synthase expression in; enzyme-catalyzed therapeutic activation, tetrahydropyrimidine derivative prodrugs, and preparation and antitumor activity)

IT Antitumor agents
(colon carcinoma; enzyme-catalyzed therapeutic activation, tetrahydropyrimidine derivative prodrugs, and preparation and antitumor activity)

IT Intestine, neoplasm
(colon, carcinoma, inhibitors; enzyme-catalyzed therapeutic activation, tetrahydropyrimidine derivative prodrugs, and preparation and antitumor activity)

IT Intestine, neoplasm
(colon, carcinoma, thymidylate synthase expression in; enzyme-catalyzed therapeutic activation, tetrahydropyrimidine derivative prodrugs, and preparation and antitumor activity)

IT Intestine
(colon, epithelium, thymidylate synthase expression in; enzyme-catalyzed therapeutic activation, tetrahydropyrimidine derivative prodrugs, and preparation and antitumor activity)

IT Intestine
(colon, thymidylate synthase expression in; enzyme-catalyzed therapeutic activation, tetrahydropyrimidine derivative prodrugs, and preparation and antitumor activity)

IT Antitumor agents
Chemotherapy
Cytotoxic agents
Drug delivery systems
Drug resistance
Drug screening
Phosphorylation, biological
(enzyme-catalyzed therapeutic activation, tetrahydropyrimidine derivative prodrugs, and preparation and antitumor activity)

IT Enzymes, biological studies
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(enzyme-catalyzed therapeutic activation, tetrahydropyrimidine derivative prodrugs, and preparation and antitumor activity)

IT Antitumor agents
(fibrosarcoma; enzyme-catalyzed therapeutic activation, tetrahydropyrimidine derivative prodrugs, and preparation and antitumor activity)

IT Antitumor agents
(mammary gland adenocarcinoma; enzyme-catalyzed therapeutic activation, tetrahydropyrimidine derivative prodrugs, and preparation and antitumor activity)

IT Drug delivery systems
(prodrugs; enzyme-catalyzed therapeutic activation, tetrahydropyrimidine derivative prodrugs, and preparation and antitumor activity)

IT Proliferation inhibition
(proliferation inhibitors; enzyme-catalyzed therapeutic activation, tetrahydropyrimidine derivative prodrugs, and preparation and antitumor activity)

IT Intestine
(small, thymidylate synthase expression in; enzyme-catalyzed therapeutic activation, tetrahydropyrimidine derivative prodrugs, and preparation and antitumor activity)

IT Prostate gland
(stroma, thymidylate synthase expression in; enzyme-catalyzed therapeutic activation, tetrahydropyrimidine derivative prodrugs, and preparation and antitumor activity)

IT Adrenal gland
Bone
Bone marrow
Brain
Fibroblast
Heart
Kidney
Liver
Lung
Muscle
Osteoblast
Ovary
Prostate gland
Salivary gland
Skin
Spleen
Stomach
Testis
Thyroid gland
Uterus
(thymidylate synthase expression in; enzyme-catalyzed therapeutic activation, tetrahydropyrimidine derivative prodrugs, and preparation and antitumor activity)

IT 82768-44-3, 5-(2-Bromovinyl)-2'-deoxyuridine
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); PROC (Process); RACT (Reactant or reagent); USES (Uses)
(enzyme-catalyzed therapeutic activation, tetrahydropyrimidine derivative prodrugs, and preparation and antitumor activity)

IT 9031-61-2, Thymidylate synthase
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(enzyme-catalyzed therapeutic activation, tetrahydropyrimidine derivative prodrugs, and preparation and antitumor activity)

IT 322454-13-7P 322454-17-1P **322454-65-9P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological

study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(enzyme-catalyzed therapeutic activation, tetrahydropyrimidine derivative prodrugs, and preparation and antitumor activity)

IT 951-78-0 61135-33-9 74131-08-1 151362-01-5 322453-87-2D, halo and cyano derivs. 322453-88-3 322453-89-4 322453-90-7D, halo and cyano derivs. 322453-91-8 322453-92-9 322453-93-0D, halo and cyano derivs. 322453-94-1 322453-96-3 322453-98-5 322454-00-2 322454-02-4 322454-02-4D, analogs 322454-04-6 322454-04-6D, analogs 322454-08-0 322454-10-4 322454-10-4D, analogs 322454-15-9 322454-19-3 322454-21-7 322454-23-9 322454-23-9D, analogs 322454-26-2 322454-26-2D, analogs 322454-29-5 322454-29-5D, analogs 322454-32-0 322454-32-0D, analogs 322454-35-3 322454-35-3D, analogs 322454-69-3 322454-75-1 322454-78-4 322454-85-3
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(enzyme-catalyzed therapeutic activation, tetrahydropyrimidine derivative prodrugs, and preparation and antitumor activity)

IT 83378-41-0
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence)
(enzyme-catalyzed therapeutic activation, tetrahydropyrimidine derivative prodrugs, and preparation and antitumor activity)

IT 157085-09-1P 321982-20-1P 321982-22-3P 321982-24-5P 321982-26-7P 321982-28-9P 321982-30-3P 321982-34-7P
RL: SPN (Synthetic preparation); PREP (Preparation)
(enzyme-catalyzed therapeutic activation, tetrahydropyrimidine derivative prodrugs, and preparation and antitumor activity)

IT 142629-80-9P 322454-46-6P 322454-48-8P 322454-51-3P 322454-53-5P 322454-55-7P 322454-59-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction; enzyme-catalyzed therapeutic activation, tetrahydropyrimidine derivative prodrugs, and preparation and antitumor activity)

IT 54-42-2 100-02-7, 4-Nitrophenol, reactions 110-87-2, 3,4-Dihydro-2H-pyran 770-12-7 1099-45-2, (Carbethoxymethylene)triphenylphosphorane 1515-75-9, Methyl 2,4-pentadienoate 2491-20-5, L-Alanine methyl ester hydrochloride 77875-99-1 96244-97-2
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction; enzyme-catalyzed therapeutic activation, tetrahydropyrimidine derivative prodrugs, and preparation and antitumor activity)

IT 51-21-8, 5-Fluorouracil 112887-68-0, Tomudex
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(tumor cell resistant to; enzyme-catalyzed therapeutic activation, tetrahydropyrimidine derivative prodrugs, and preparation and antitumor activity)

IT 322773-91-1, 1: PN: WO0107454 SEQID: 1 unclaimed DNA 322773-92-2, 2: PN: WO0107454 SEQID: 2 unclaimed DNA 322773-93-3, 3: PN: WO0107454 SEQID: 3 unclaimed DNA 322773-94-4, 4: PN: WO0107454 SEQID: 4 unclaimed DNA
RL: PRP (Properties)
(unclaimed nucleotide sequence; enzyme-catalyzed therapeutic activation, tetrahydropyrimidine derivative prodrugs, and preparation and antitumor activity thereof)

RE.CNT 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

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(2) Anderson, L; WO 9923104 A 1999 HCAPLUS
(3) Bergstrom, D; J MED CHEM 1984, V27, P279 HCAPLUS
(4) Budavari; The Merck index 1996
(5) Budavari; The Merck index 1996
(6) Budavari; The Merck index 1996
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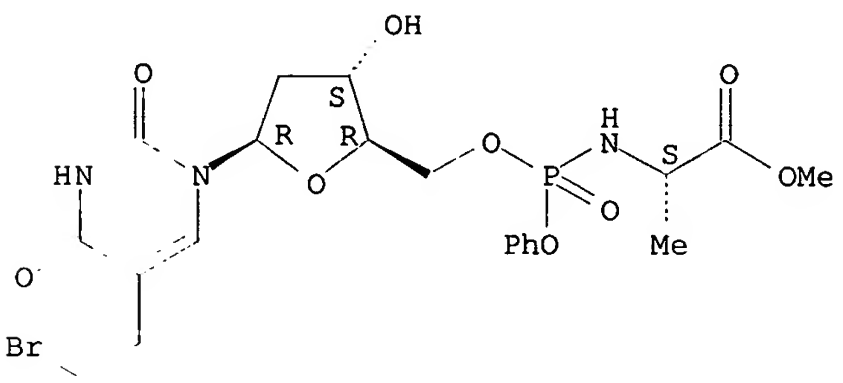
(9) Goodwin; TETRAHEDRON LETTERS 1993, V34(35), P5549 HCAPLUS

(10) Groziak, M; WO 9937753 A 1999 HCAPLUS
(11) Robins, M; JOURNAL OF ORGANIC CHEMISTRY 1983, V48(11), P1854 HCAPLUS
(12) Shepard, H; WO 9908110 A 1999 HCAPLUS
IT **322454-65-9P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(enzyme-catalyzed therapeutic activation, tetrahydropyrimidine derivative prodrugs, and preparation and antitumor activity)
RN 322454-65-9 HCAPLUS
CN L-Alanine, N-[5-(2-bromoethenyl)-2'-deoxy-P-phenyl-5'-uridylyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



L24 ANSWER 7 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2002:153907 HCAPLUS
DN 137:27792
ED Entered STN: 28 Feb 2002
TI Synthesis and antiviral evaluation of phosphoramidate derivatives of (E)-5-(2-bromovinyl)-2'-deoxyuridine
AU Harris, S. A.; McGuigan, C.; Andrei, G.; Snoeck, R.; De Clercq, E.; Balzarini, J.
CS Welsh School of Pharmacy, Cardiff University, Cardiff, UK
SO Antiviral Chemistry & Chemotherapy (**2001**), 12(5), 293-300
CODEN: ACCHEH; ISSN: 0956-3202
PB International Medical Press
DT Journal
LA English
CC 1-3 (Pharmacology)
OS CASREACT 137:27792
AB We report the design, synthesis and antiviral evaluation of a number of lipophilic, masked phosphoramidate derivs. of the antiherpetic agent (E)-5-(2-bromovinyl)-2'-deoxyuridine (BVDU), designed to act as membrane soluble prodrugs of the free nucleotide. The phosphoramidate derivs. of BVDU that contain L-alanine exhibited potent anti herpes simplex virus type 1 and varicella-zoster virus activity but lost marked activity against thymidine kinase-deficient virus strains. The phosphoramidate derivative bearing the amino acid α,α-dimethylglycine showed poor activity in all cell lines tested. It appears that successful kinase bypass by phosphoramidates is highly dependent on the nucleoside analog, amino acid and ester structure, as well as the cell line to which the drugs are exposed.
ST antiviral antiherpetic phosphoramidate deriv design nucleotide prodrug
IT Drug resistance
Structure-activity relationship
(antiviral; synthesis and antiviral evaluation of phosphoramidate derivs. of (E)-5-(2-bromovinyl)-2'-deoxyuridine)
IT Antiviral agents
(resistance to; synthesis and antiviral evaluation of phosphoramidate derivs. of (E)-5-(2-bromovinyl)-2'-deoxyuridine)
IT Antiviral agents
Drug design
Human

Human herpesvirus 1
Human herpesvirus 2
Human herpesvirus 3
(synthesis and antiviral evaluation of phosphoramidate derivs. of (E)-5-(2-bromovinyl)-2'-deoxyuridine)

IT 9002-06-6, Thymidine kinase 59277-89-3, Acyclovir
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(synthesis and antiviral evaluation of phosphoramidate derivs. of (E)-5-(2-bromovinyl)-2'-deoxyuridine)

IT **232925-18-7P** 436097-54-0P 436097-55-1P
RL: PAC (Pharmacological activity); PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(synthesis and antiviral evaluation of phosphoramidate derivs. of (E)-5-(2-bromovinyl)-2'-deoxyuridine)

IT 69304-47-8
RL: PAC (Pharmacological activity); PRP (Properties); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)
(synthesis and antiviral evaluation of phosphoramidate derivs. of (E)-5-(2-bromovinyl)-2'-deoxyuridine)

IT 436097-56-2P
RL: PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(synthesis and antiviral evaluation of phosphoramidate derivs. of (E)-5-(2-bromovinyl)-2'-deoxyuridine)

IT 106-48-9, 4-Chlorophenol 770-12-7, Phenyl dichlorophosphate 772-79-2, p-Chlorophenyl phosphorodichloridate 2491-20-5, L-Alanine methylester hydrochloride 5557-83-5, L-Alanine benzylester hydrochloride 10025-87-3, Phosphorus oxychloride 15028-41-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(synthesis and antiviral evaluation of phosphoramidate derivs. of (E)-5-(2-bromovinyl)-2'-deoxyuridine)

IT 142629-80-9P 183370-70-9P 217090-41-0P 261909-35-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis and antiviral evaluation of phosphoramidate derivs. of (E)-5-(2-bromovinyl)-2'-deoxyuridine)

RE.CNT 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Allaudeen, H; Proceedings of the National Academy of Sciences, USA 1981, V78, P2698 HCAPLUS
(2) Alrabiah, F; Drugs 1996, V52, P17 HCAPLUS
(3) Andrei, G; European Journal of Clinical Microbiology and Infectious Diseases 1992, V11, P143 HCAPLUS
(4) Balzarini, J; FEBS Letters 1997, V410, P324 HCAPLUS
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(19) Pottage, J; Infectious Agents and Disease - Reviews Issue and Commentary 1995, V4, P115 HCAPLUS
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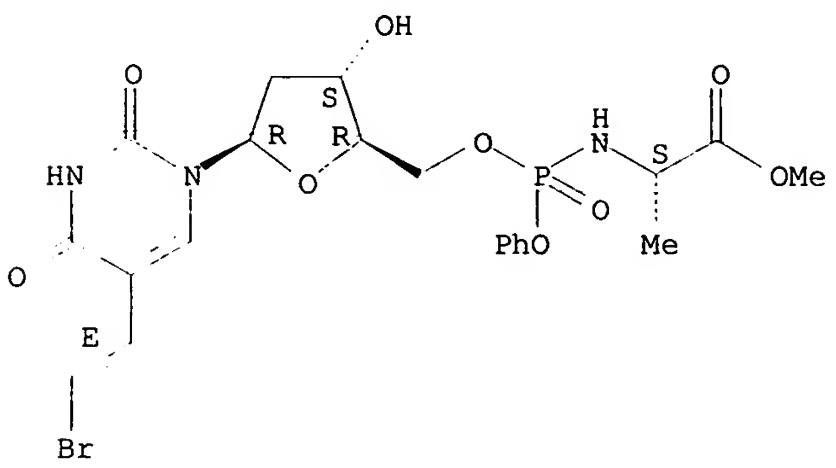
(23) Wutzler, P; Intervirology 1997, V40, P343 HCAPLUS
IT **232925-18-7P**
RL: PAC (Pharmacological activity); PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(synthesis and antiviral evaluation of phosphoramidate derivs. of (E)-5-(2-bromovinyl)-2'-deoxyuridine)
RN 232925-18-7 HCAPLUS
CN L-Alanine, N-[5-[(1E)-2-bromoethenyl]-2'-deoxy-P-phenyl-5'-uridylyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L24 ANSWER 8 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1999:487370 HCAPLUS
DN 131:111426
ED Entered STN: 06 Aug 1999
TI Method for drug screening and enzyme-activated phosphoryl or phosphoramidate prodrugs and their synthesis and use in inhibition of cell proliferation
IN **Shepard, H. Michael**; Groziak, Michael P.
PA **Newbiotics, Inc., USA**
SO PCT Int. Appl., 113 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C12N009-10
ICS C12N009-12; C12N005-18; C07H019-04; C07H019-06; C07H019-044; A61K051-00; A01N043-04
CC 1-6 (Pharmacology)
Section cross-reference(s): 33
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9937753	A1	19990729	WO 1999-US1332	19990122 <--
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	CA 2317505	AA	19990729	CA 1999-2317505	19990122 <--
	AU 9924646	A1	19990809	AU 1999-24646	19990122 <--
	AU 753155	B2	20021010		
	BR 9907736	A	20001017	BR 1999-7736	19990122 <--
	EP 1045897	A1	20001025	EP 1999-904195	19990122 <--
	EP 1045897	B1	20020130		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

	US 6245750	B1	20010612	US 1999-235809	19990122 <--
	EP 1167972	A2	20020102	EP 2001-120242	19990122 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	JP 2002500880	T2	20020115	JP 2000-528661	19990122 <--
	AT 212661	E	20020215	AT 1999-904195	19990122 <--
	PT 1045897	T	20020731	PT 1999-904195	19990122 <--
	ES 2172303	T3	20020916	ES 1999-904195	19990122 <--
	JP 2001220397	A2	20010814	JP 2000-339831	20001108 <--
	JP 3265304	B2	20020311		
	HK 1030624	A1	20020614	HK 2001-100891	20010208 <--
PRAI	US 1998-72264P	P	19980123 <--		
	US 1998-76950P	P	19980305 <--		
	US 1998-108634P	P	19981116 <--		
	EP 1999-904195	A3	19990122 <--		
	JP 2000-528661	A3	19990122 <--		
	WO 1999-US1332	W	19990122 <--		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES	
WO 9937753	ICM	C12N009-10	
	ICS	C12N009-12; C12N005-18; C07H019-04; C07H019-06; C07H019-044; A61K051-00; A01N043-04	
WO 9937753	ECLA	A61K047/48H4; C07F009/6512G; C07H019/06E	<--
US 6245750	ECLA	A61K047/48H4	<--
EP 1167972	ECLA	A61K047/48H4	<--

OS CASREACT 131:111426; MARPAT 131:111426

AB This invention provides a method for identifying potential therapeutic agents by contacting a target cell with a candidate therapeutic agent which is a selective substrate for an endogenous, intracellular enzyme in the cell which is enhanced in its expression as a result of selection by biol. or chemotherapy. This invention also provides methods and examples of mols. for selectively killing a pathol. cell by contacting the cell with a prodrug that is a selective substrate for an endogenous, intracellular enzyme. The prodrug is subsequently converted to a cellular toxin. Further provided by this invention is a method for treating a pathol. characterized by pathol., hyperproliferative cells in a subject by administering to the subject a prodrug that is a selective substrate for an endogenous, overexpressed, intracellular enzyme, and converted by the enzyme to a cellular toxin in the hyperproliferative cell. Thus, E-5-(2-bromovinyl)-2'-deoxy-5'-uridyl Ph L-alaninylphosphoramidate (BVDU-PA) was prepared by reacting E-5-(2-bromovinyl)-2'-deoxyuridine with Ph L-methoxyalaninyl phosphorochloridate in anhydrous DMF in the presence of imidazole (HCl scavenger). BVDU-PA was added to H630R10 cells and to CCD18co control cells. H630R10 cells expressed 10-fold more thymidylate synthase enzyme than CCD18co cells. BVDU-PA displayed IC50's of 217 and 2810 μM on the H630R10 cells and CCD18co cells, resp.

ST enzyme activated phosphoryl phosphoramidate prodrug synthesis cytostatic; thymidylate synthase bromovinyl deoxyuridine phosphoramidate tumor inhibitor

IT Cell proliferation
(inhibition of; method for drug screening and enzyme-activated phosphoryl or phosphoramidate prodrugs and their synthesis and use in inhibition of cell proliferation)

IT Antitumor agents
Cytotoxic agents
Drug screening
(method for drug screening and enzyme-activated phosphoryl or phosphoramidate prodrugs and their synthesis and use in inhibition of cell proliferation)

IT Enzymes, biological studies
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(overexpressed in target cell; method for drug screening and enzyme-activated phosphoryl or phosphoramidate prodrugs and their synthesis and use in inhibition of cell proliferation)

IT Animal cell
(prodrug screening with; method for drug screening and enzyme-activated

phosphoryl or phosphoramidate prodrugs and their synthesis and use in inhibition of cell proliferation)

IT Drug delivery systems
(prodrugs; method for drug screening and enzyme-activated phosphoryl or phosphoramidate prodrugs and their synthesis and use in inhibition of cell proliferation)

IT 288-32-4, Imidazole, reactions
RL: RCT (Reactant); RACT (Reactant or reagent)
(HCl scavenger in prodrug synthesis; method for drug screening and enzyme-activated phosphoryl or phosphoramidate prodrugs and their synthesis and use in inhibition of cell proliferation)

IT 9031-61-2, Thymidylate synthase
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(method for drug screening and enzyme-activated phosphoryl or phosphoramidate prodrugs and their synthesis and use in inhibition of cell proliferation)

IT 951-78-0DP, 2'-Deoxyuridine, phosphoramidate derivs.
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(method for drug screening and enzyme-activated phosphoryl or phosphoramidate prodrugs and their synthesis and use in inhibition of cell proliferation)

IT **232925-18-7P** 232925-20-1P
RL: BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(method for drug screening and enzyme-activated phosphoryl or phosphoramidate prodrugs and their synthesis and use in inhibition of cell proliferation)

IT 232925-21-2 232925-22-3 232925-23-4
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(method for drug screening and enzyme-activated phosphoryl or phosphoramidate prodrugs and their synthesis and use in inhibition of cell proliferation)

IT 69304-47-8, BVDU 142629-80-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(method for drug screening and enzyme-activated phosphoryl or phosphoramidate prodrugs and their synthesis and use in inhibition of cell proliferation)

RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

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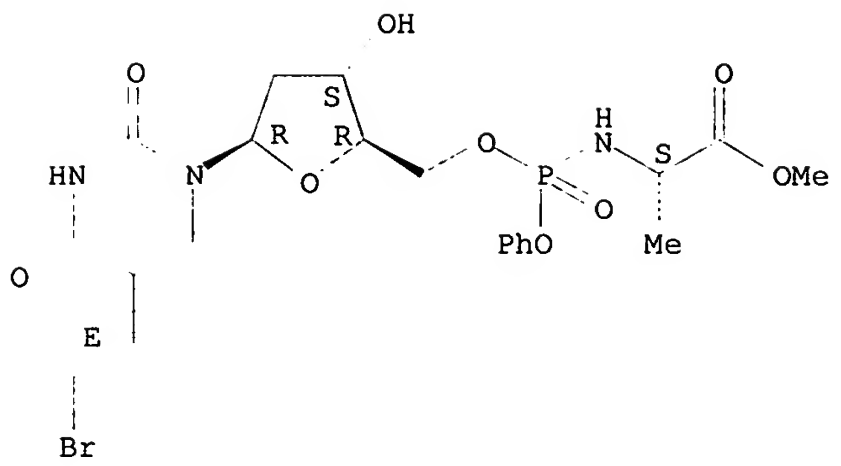
(2) Goldberg; Am J Respir Cell Mol Biol 1997, V17, P265 HCAPLUS
(3) Pardo; Exp Cell Res 1987, V168, P507 HCAPLUS

IT **232925-18-7P**
RL: BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(method for drug screening and enzyme-activated phosphoryl or phosphoramidate prodrugs and their synthesis and use in inhibition of cell proliferation)

RN 232925-18-7 HCAPLUS

CN L-Alanine, N-[5-[(1E)-2-bromoethenyl]-2'-deoxy-P-phenyl-5'-uridylyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L24 ANSWER 9 OF 14 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN
AN 2001:299617 BIOSIS
DN PREV200100299617
TI Characterization of intracellular transformations of **NB1011**: A novel anti-cancer agent that is preferentially cytotoxic in tumor cells.
AU Sergeeva, Maria V. [Reprint author]; Gathers, Brian E. [Reprint author]; Lackey, David B. [Reprint author]; Shepard, H. Michael [Reprint author]
CS NewBiotics, Inc., 11760-E Sorrento Valley Rd., San Diego, CA, 92121, USA
SO FASEB Journal, (March 7, 2001) Vol. 15, No. 4, pp. A554. print.
Meeting Info.: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001. Orlando, Florida, USA. March 31-April 04, 2001.
CODEN: FAJOEC. ISSN: 0892-6638.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 20 Jun 2001
Last Updated on STN: 19 Feb 2002
AB Thymidylate synthase (TS) is overexpressed in tumor cells which gives rise to the resistance of tumors to TS inhibitors used for the treatment of colon and other intestinal cancers. A different approach, called Enzyme Catalyzed Therapeutic Activation (ECTA), developed at NewBiotics, utilizes lead compounds that are not TS inhibitors but TS substrates. TS ECTA compounds can undergo a transformation catalyzed by TS to generate cytotoxic reaction product(s) which are preferentially produced inside TS overexpressing tumor cells. Therefore, TS ECTA compounds are cytotoxic to tumor cells and have little effect on normal cells. The ECTA approach is anticipated to overcome drug resistance and have low toxic side effects. **NB1011**, a TS ECTA compound, is a phosphoramidate of E-5-(2-bromovinyl)-2'-deoxyuridine. The phosphoramidate moiety of the molecule was designed to supply a corresponding monophosphate (BVdUMP) to the cells without the necessity of the nucleoside phosphorylation by human thymidine kinase (TK) which is a poor catalyst of the phosphorylation of unnatural nucleosides.. We have studied the mechanism of **NB1011** transformation inside the cell and have detected the formation of BVdUMP, a substrate of TS. In order to determine the mechanism of TS reaction with BVdUMP in vivo we have extensively studied the catalytic activity of TS towards BVdUMP in a cell-free system under various conditions which included variation of nucleophiles present in the reaction mixture and mimicking the intracellular environment. To determine the mechanism of **NB1011** toxicity in cell based systems we have used an analog of **NB1011** labeled with 14C in the base (2-position). The experiments to identify the major metabolites of **NB1011** downstream of TS and to determine 14C incorporation into major subcellular fractions (DNA, RNA, and proteins) are being carried out.
CC Neoplasms - Therapeutic agents and therapy 24008
General biology - Symposia, transactions and proceedings 00520
Cytology - Animal 02506
Enzymes - General and comparative studies: coenzymes 10802
Pathology - Therapy 12512
Cardiovascular system - Physiology and biochemistry 14504

Pharmacology - General 22002
Neoplasms - Pathology, clinical aspects and systemic effects 24004
IT Major Concepts
Pharmacology; Cardiovascular System (Transport and Circulation); Tumor Biology
IT Parts, Structures, & Systems of Organisms
tumor cell
IT Chemicals & Biochemicals
NB1011: antineoplastic-drug, intracellular transformations, pharmacodynamics, preferential cytotoxicity; thymidylate synthase: expression
IT Methods & Equipment
Enzyme Catalyzed Therapeutic Activation: pharmacological method
IT Miscellaneous Descriptors
drug development; Meeting Abstract
RN **232925-18-7 (NB1011)**
9031-61-2 (thymidylate synthase)

L24 ANSWER 10 OF 14 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN
AN 2001:468786 BIOSIS
DN PREV200100468786
TI **NB1011**, a novel drug that targets tumor cells overexpressing thymidilate synthase, induces p21, BAX and GADD45 and blocks G2/M cell cycle progression in MCF7TDX cells.
AU Boyer, Christopher R. [Reprint author]; Li, Qing; Karjian, Patricia L.; Lee, Jean; Wahl, Geoffrey M.; Neuteboom, Saskia T. C.
CS NewBiotics Inc., San Diego, CA, USA
SO Proceedings of the American Association for Cancer Research Annual Meeting, (March, 2001) Vol. 42, pp. 507-508. print.
Meeting Info.: 92nd Annual Meeting of the American Association for Cancer Research. New Orleans, LA, USA. March 24-28, 2001.
ISSN: 0197-016X.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 3 Oct 2001
Last Updated on STN: 23 Feb 2002
CC General biology - Symposia, transactions and proceedings 00520
Cytology - Human 02508
Enzymes - General and comparative studies: coenzymes 10802
Pathology - Therapy 12512
Pharmacology - General 22002
Pharmacology - Clinical pharmacology 22005
Neoplasms - Pathology, clinical aspects and systemic effects 24004
IT Major Concepts
Pharmacology; Tumor Biology
IT Chemicals & Biochemicals
BAX protein: drug-induced tumor cell expression; GADD-45 protein: drug-induced tumor cell expression; **NB 1011**: antineoplastic-drug, enzyme inhibitor-drug; p-21 protein: drug-induced tumor cell expression; thymidylate synthase: drug-induced inhibition, tumor cell overexpression
IT Miscellaneous Descriptors
Meeting Abstract
ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
MCF-7TDX cell line: drug-induced G-2-mitosis cell cycle progression block, human breast cancer cell line, in-vitro model system
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates
RN **232925-18-7 (NB 1011)**
9031-61-2 (thymidylate synthase)

L24 ANSWER 11 OF 14 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN

AN 2001:468752 BIOSIS
DN PREV200100468752
TI Nucleoside transport inhibitors, dipyridamole and P-nitrobenzylthioinosine, selectively potentiate the activity of **NB1011** against human tumor cell lines expressing high levels of thymidylate synthase.
AU Boyer, Christopher R. [Reprint author]; Karjian, Patricia L.; Wahl, Geoffrey M.; Neuteboom, Saskia T. C.
CS NewBiotics, Inc., San Diego, CA, USA
SO Proceedings of the American Association for Cancer Research Annual Meeting, (March, 2001) Vol. 42, pp. 296. print.
Meeting Info.: 92nd Annual Meeting of the American Association for Cancer Research. New Orleans, LA, USA. March 24-28, 2001.
ISSN: 0197-016X.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 3 Oct 2001
Last Updated on STN: 23 Feb 2002
CC General biology - Symposia, transactions and proceedings 00520
Cytology - Human 02508
Biochemistry studies - General 10060
Biochemistry studies - Nucleic acids, purines and pyrimidines 10062
Enzymes - General and comparative studies: coenzymes 10802
Pathology - Therapy 12512
Pharmacology - General 22002
Pharmacology - Clinical pharmacology 22005
Neoplasms - Pathology, clinical aspects and systemic effects 24004
IT Major Concepts
Enzymology (Biochemistry and Molecular Biophysics); Pharmacology; Tumor Biology
IT Chemicals & Biochemicals
5-fluorouracil: antineoplastic-drug; **NB1011**: antineoplastic-drug, efficacy; Tomudex: antineoplastic-drug; dipyridamole: antineoplastic-drug, nucleoside transport inhibitor, potency; para-nitrobenzylthioinosine: antineoplastic-drug, nucleoside transport inhibitor, potency; thymidylate synthase: expression
IT Methods & Equipment
CalcuSyn software: computer software
IT Miscellaneous Descriptors
cell survival; drug resistance; drug synergism; Meeting Abstract
ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
CCD18co cell line: human colon epithelial cells
Det551 cell line: human embryonic skin fibroblast cells
H630R10 cell line: human colon carcinoma cells
MCF7TDX cell line: human breast adenocarcinoma cells
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates
RN 51-21-8 (5-fluorouracil)
232925-18-7 (NB1011)
112887-68-0 (Tomudex)
58-32-2 (dipyridamole)
9031-61-2 (thymidylate synthase)

L24 ANSWER 12 OF 14 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN
AN 2001:459023 BIOSIS
DN PREV200100459023
TI **Nb1011**, a novel drug that targets tumor cells overexpressing thymidylate synthase, induces P21, BAX and GADD45 and blocks G2/M cell cycle progression in MCF7TDX cells.
AU Neuteboom, S. T. C. [Reprint author]; Boyer, C. R. [Reprint author]; Karjian, P. L. [Reprint author]; Wahl, G. M. [Reprint author]
CS NewBiotics, Inc., San Diego, CA, USA
SO International Journal of Antimicrobial Agents, (June, 2001) Vol. 17, No.

Supplement 1, pp. S108. print.
Meeting Info.: 22nd International Congress of Chemotherapy. Amsterdam, Netherlands. June 30-July 03, 2001.
ISSN: 0924-8579.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 26 Sep 2001
Last Updated on STN: 22 Feb 2002
CC General biology - Symposia, transactions and proceedings 00520
Cytology - Animal 02506
Cytology - Human 02508
Biochemistry studies - Nucleic acids, purines and pyrimidines 10062
Biochemistry studies - Proteins, peptides and amino acids 10064
Enzymes - General and comparative studies: coenzymes 10802
Pathology - Therapy 12512
Pharmacology - General 22002
Pharmacology - Clinical pharmacology 22005
Neoplasms - Pathology, clinical aspects and systemic effects 24004
IT Major Concepts
Enzymology (Biochemistry and Molecular Biophysics); Pharmacology; Tumor Biology
IT Parts, Structures, & Systems of Organisms
tumor cells
IT Chemicals & Biochemicals
Bax proteins; DNA: biosynthesis; GADD45; **Nb1011**: antineoplastic agent, pharmaceutical, pharmacodynamics, uses; RNA; p21 proteins; proteins; thymidylate synthase: analysis, functions, inhibition, overexpression
IT Miscellaneous Descriptors
G2/M cell cycle progression: blockage; apoptosis; Meeting Abstract
ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
MCF7TDX cell line
human
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates
RN **232925-18-7 (Nb1011)**
9031-61-2 (thymidylate synthase)

L24 ANSWER 13 OF 14 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN
AN 2000:198618 BIOSIS
DN PREV200000198618
TI Thymidylate synthase catalyzes generation of cytotoxic species preferentially inside tumor cells.
AU Li, Qing [Reprint author]; Sergeeva, Maria [Reprint author]; Boyer, Christopher [Reprint author]; Lee, Jean [Reprint author]; Lackey, David [Reprint author]; Shepard, H. Michael [Reprint author]
CS NewBiotics, Inc, San Diego, CA, USA
SO Proceedings of the American Association for Cancer Research Annual Meeting, (March, 2000) No. 41, pp. 5-6. print.
Meeting Info.: 91st Annual Meeting of the American Association for Cancer Research. San Francisco, California, USA. April 01-05, 2000.
ISSN: 0197-016X.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 17 May 2000
Last Updated on STN: 4 Jan 2002
CC Pathology - Therapy 12512
Digestive system - Pathology 14006
Pharmacology - Clinical pharmacology 22005
Neoplasms - Therapeutic agents and therapy 24008
Neoplasms - Pathology, clinical aspects and systemic effects 24004
General biology - Symposia, transactions and proceedings 00520

IT Major Concepts
Pharmacology; Tumor Biology
IT Diseases
colon cancer: digestive system disease, neoplastic disease, drug treatment, in-vitro cell study
Colonic Neoplasms (MeSH)
IT Chemicals & Biochemicals
5-bromovinyldeoxy-UMP [**NB-1011**]:
antineoplastic-drug, thymidylate synthase-catalyzed cytotoxic species generation
IT Miscellaneous Descriptors
Meeting Abstract
ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human: patient
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

L24 ANSWER 14 OF 14 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN
AN 2001099014 EMBASE
TI Trojan antibiotics.
AU Habeck M.
SO Drug Discovery Today, (1 Apr 2001) 6/7 (330-331).
Refs: 1
ISSN: 1359-6446 CODEN: DDTOFS
PUI S 1359-6446(01)01745-7
CY United Kingdom
DT Journal; (Short Survey)
FS 037 Drug Literature Index
004 Microbiology
LA English
CT Medical Descriptors:
*antimicrobial activity
*drug development
*bactericidal activity
*breast cancer
*colorectal cancer
drug resistance
drug efficacy
human
short survey
Drug Descriptors:
*antibiotic agent: PD, pharmacology
*antibiotic agent: DV, drug development
*triclosan: PD, pharmacology
*triclosan: DV, drug development
*cephalosporin: PD, pharmacology
*cephalosporin: DV, drug development
nb 2001: PD, pharmacology
nb 2001: DV, drug development
nb 1011: PD, pharmacology
nb 1011: DV, drug development
unclassified drug
RN (triclosan) 3380-34-5; (cephalosporin) 11111-12-9

=> fil uspatful
FILE 'USPATFULL' ENTERED AT 10:20:53 ON 17 FEB 2005
CA INDEXING COPYRIGHT (C) 2005 AMERICAN CHEMICAL SOCIETY (ACS)

FILE COVERS 1971 TO PATENT PUBLICATION DATE: 15 Feb 2005 (20050215/PD)
FILE LAST UPDATED: 15 Feb 2005 (20050215/ED)
HIGHEST GRANTED PATENT NUMBER: US6857132
HIGHEST APPLICATION PUBLICATION NUMBER: US2005034203
CA INDEXING IS CURRENT THROUGH 15 Feb 2005 (20050215/UPCA)

ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 15 Feb 2005 (20050215/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Dec 2004
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Dec 2004

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>>> publications, starting in 2001, for the inventions covered in <<<
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>>> publications. The publication number, patent kind code, and <<<
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>>> records and may be searched in standard search fields, e.g., /PN, <<<
>>> /PK, etc. <<<

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>>> through the new cluster USPATALL. Type FILE USPATALL to <<<
>>> enter this cluster. <<<
>>> <<<
>>> Use USPATALL when searching terms such as patent assignees, <<<
>>> classifications, or claims, that may potentially change from <<<
>>> the earliest to the latest publication. <<<

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> => d bib abs kwic hitstr tot l16

L16 ANSWER 1 OF 10 USPATFULL on STN
AN 2004:21602 USPATFULL
TI Enzyme catalyzed therapeutic activation
IN Shepard, H. Michael, Encinitas, CA, United States
Chan, Ming Fai, Encinitas, CA, United States
Groziak, Michael P., Palo Alto, CA, United States
PA NewBiotics, Inc., San Diego, CA, United States (U.S. corporation)
PI US 6683061 B1 20040127
WO 2001007454 20010201
AI US 2001-856127 20011010 (9)
WO 2000-US20008 20000721 <--
PRAI US 1999-145356P 19990722 (60) <--
US 1999-145437P 19990723 (60) <--
US 2000-191315P 20000321 (60) <--
DT Utility
FS GRANTED
EXNAM Primary Examiner: Wilson, James O.; Assistant Examiner: Lewis, Patrick
LREP Konski, Antoinette F., Bingham McCutchen LLP
CLMN Number of Claims: 10
ECL Exemplary Claim: 1
DRWN 7 Drawing Figure(s); 6 Drawing Page(s)
LN.CNT 2653
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention provides novel substrate compounds that selectively inhibit the proliferation of pathological cells, for example, pathological calls that endogenously overexpress a target enzyme that confers resistance to biologic and chemotherapeutic agents. The enzyme acts on a substrate compound to 1) convert it to a cellular toxin and/or 2) release a toxic byproduct. In one embodiment, the activity of the target enzyme has been greatly enhanced in a target cell as a result of loss of tumor suppressor function and/or selection resulting from previous exposure to chemotherapy. In another embodiment, the pathological cell contains a target enzyme that is an expression product of an infectious agent in the cell. Further provided by this invention is a method for treating a subject by delivering to the subject a prodrug as described herein. The prodrugs of this invention may be used alone or in combination with other chemotherapeutics or alternative anti-cancer therapies such as radiation.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AI US 2001-856127 20011010 (9)
WO 2000-US20008 20000721 <--
PRAI US 1999-145356P 19990722 (60) <--
PRAI US 1999-145437P 19990723 (60) <--
PRAI US 2000-191315P 20000321 (60) <--
DRWD . . . herein are displayed graphically in FIGS. 1A and 1B using the example of the thymidylate synthase enzyme and the compound **NB1011**.TM..
DRWD . . . higher levels of TS in tumor cells can lead to preferential generation of toxin. FIG. 1B shows the conversion of **NB1011** .TM. to BVdUMP, and subsequent interaction with TS to generate nucleotide toxin.
DETD . . . above are displayed graphically in FIG. 1A and 1B using the example of the thymidylate synthase enzyme and the compound **NB1011**.TM..
DETD

##STR29##

R ##STR30## Y = H

##STR31## **NB1011** NB1015 (BVdU)

##STR32## NB1012 --

##STR33## NB1013 NB1020

--CF.sub.3 BN1014 NB1027

##STR34## NB1016 NB1021

##STR35## NB1017. . .
DETD 5-(2-Bromovinyl)-2'-Deoxyuridine Phenyl N-Methoxy-L-alaninyl Phosphoramidate (**NB1011**)
DETD . . . L of dichloromethane and passed through 800 g of silica gel. The major portion of BVdU-PA referred to herein as **NB1011**, was passed through the column during the loading and finally the elution of **NB1011** was completed by passing 5 L of 5% methanol in dichloromethane. All fractions containing **NB1011** were combined and evaporated to an oil, the residue was dissolved in 4 L of ethyl acetate and the mixture. . .
DETD This assay was performed with the compound **NB 1011.** However, it understood to those of skill in the art that the below method is easily modified for application or. . .
DETD This assay was performed with the compound **NB1011** and the prodrugs of this invention. Cells growing exponentially were transferred to 384-well flat bottom tissue culture plates. All cell. . .
DETD This assay was performed with the compound **NB1011** and the prodrugs of this invention. The ability of the test compounds to block proliferation of cells was determined by. . .
DETD . . . Blue Cytotoxicity Assay of Normal and Tumor Cells
IC50 (μM) Mean IC50 (μM) Mean
MCF7TDX H630R10 HT1080 Tumor CCd18co Det551 Normal

NB1011 2 82 182 88.7 414 398 406
BVDU 0.02 201 719 306.7 1000 ND 1000
NB1012 127 82 -- 104.5 ND 110. . .
DETD . . . Violet Assay of Normal and Tumor Cells
Mean
IC50 (uM) Mean IC50 (uM) Nor-
H630R10 HT1080 #12 Tumor CCD18co Det551 mal

NB1011 130 1.2 65.6 408 356 382
BVDU 405 7 206.0 1000 625 812.5
NB1017 111 17 64.0 206 253 229.5
NB1024 92 3.3. . .
DETD . . . phosphoramidate, but is active as a nucleoside (NB1025.TM.). This result indicates that NB 1026.TM. may not be activated similar to **NB1011**.TM.. Cytotoxicity results with the nucleosides,

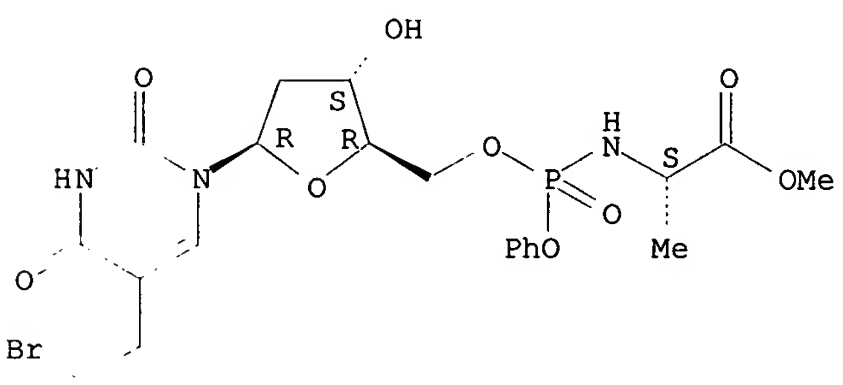
especially BVdU, NB1020.TM. (ClVdU) and NB1024.TM., are surprising since the literature teaches that 5-substituted compounds. . .

DETD
TABLE 7

Cytotoxic Activity of NB1024 Isomers
TS HT1080 #12 MCF7TDX CCD18co Det551

NB1011 4.3 4.2 461 263
BVdU ND <0.8 >1000 >1000
NB1024 Mixture 10.7 6.4 >300 >300
NB1024 Isomer 1 10.1 9.8 >300 >300
NB1024 Isomer. . .
IT 322454-13-7P 322454-17-1P **322454-65-9P**
(enzyme-catalyzed therapeutic activation, tetrahydropyrimidine derivative prodrugs, and preparation and antitumor activity)
IT **322454-65-9P**
(enzyme-catalyzed therapeutic activation, tetrahydropyrimidine derivative prodrugs, and preparation and antitumor activity)
RN 322454-65-9 USPATFULL
CN L-Alanine, N-[5-(2-bromoethenyl)-2'-deoxy-P-phenyl-5'-uridylyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



L16 ANSWER 2 OF 10 USPATFULL on STN
AN 2003:300811 USPATFULL
TI Use of bvdu for inhibiting the growth of hyperproliferative cells
IN Boyer, Christopher, San Diego, CA, UNITED STATES
Lackey, David B., San Diego, CA, UNITED STATES
PI US 2003212037 A1 20031113
AI US 2002-168722 A1 20021210 (10)
WO 2000-US35027 20001221 <--
DT Utility
FS APPLICATION
LREP Antoinette F Konski, McCutchen Doyle Brown & Enersen, 18th Floor, Three Embarcadero Center, San Francisco, CA, 94111-4067
CLMN Number of Claims: 30
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 981
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention provides methods for selectively killing a hyperproliferative cell by contacting the cell with the compound BVdU, its derivatives and pharmaceutically acceptable salts. Further provided by this invention is a method for treating a pathology in a subject characterized by pathological, hyperproliferative cells by administering to the subject an effective amount of the compound BVdU, its derivatives and pharmaceutically acceptable salts. The invention also provides a method for screening for potential therapeutic agents by contacting a neoplastic cell with the agent and with BVdU and performing an assay to detect inhibition of proliferation and cell killing. The invention also provides methods for selecting from among a patient population, patients that are likely to benefit from treatment with BVdU, by determining the

level of endogenous, intracellular TK and TS. The invention also provides methods for sensitizing patients to the therapeutic effects of BVdU by treatment with substances that result in the increase in the levels of TK in hyperproliferative cells.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AI US 2002-168722 A1 20021210 (10)
WO 2000-US35027 20001221 <--
DETD . . . complete medium (RPMI 1640+10% fetal bovine serum+antibiotics/antimyotics). After 24 hours (day 0), 25 μL of complete medium containing the compounds (**NB1011** or BVDU) over the dose range of 10.sup.-3 to 10.sup.-10 M were added in triplicate. Drug exposure time was 120. . .
DETD . . . BVdU in inhibiting the proliferation of a test cancer cell line was demonstrated by comparison with the deoxyribose nucleotide derivative **NB1011** using a cell-based assay. **NB1011** {(E)-5-(2-bromovinyl)-2'deoxyuridine phenyl L-alaninylphosphoramidate)} is a modified derivative of BVdUMP with a neutral 5'-phosphoramidates, L-phenyl L-alaninlyphosphoramidate. The process for preparing **NB 1011** is known in the art (See PCT/US99/01332).
DETD . . . cell line selected with Tomudex, and overexpresses thymidylate synthase to approximately the same extent. Both cell lines are sensitive to **NB1011** compared to normal cell strains; however, MCF7 TDX is significantly more sensitive to **NB1011** than is H630 R10. H630 R10 has previously been shown to be insensitive to BVdU.
DETD . . . IC.sub.50 using the alamarBlue cytotoxicity assay described above.
TABLE 1

Compound	H630 R10 IC.sub.50 (μM)	MCF7 TDX IC.sub.50 (μM)
NB1011	57	0.13
BVdU	303	0.005

DETD . . . indicate that BVdU is relatively inactive against H630R10 cells (fluoropyrimidine resistant colon) (303 μM IC.sub.50, .about.6 fold less active than **NB1011**). In contrast, it was found that BVdU was extremely cytotoxic against MCF7 TDX cells (Tomudex resistant breast cancer cell line), (5 nM IC.sub.50, .about.25-fold more active than **NB1011**. This finding shows that a class of tumor cells exists with sensitivity to BVdU, similar to that of MCF7 TDX. . .

L16 ANSWER 3 OF 10 USPATFULL on STN
AN 2003:188386 USPATFULL
TI Methods for identifying therapeutic targets for treating infectious disease
IN Shepard, H. Michael, Encinitas, CA, UNITED STATES
Lackey, David B., San Diego, CA, UNITED STATES
Cathers, Brian E., San Diego, CA, UNITED STATES
Sergeeva, Maria V., San Diego, CA, UNITED STATES
PI US 2003130179 A1 20030710
AI US 2001-910345 A1 20010720 (9)
PRAI US 2000-219598P 20000720 (60) <--
US 2000-244953P 20001101 (60) <--
US 2001-276728P 20010316 (60)
DT Utility
FS APPLICATION
LREP Antoinette F. Konski, McCutchen, Doyle, Brown & Enersen, LLP, 18th Floor, Three Embarcadero Center, San Francisco, CA, 94111
CLMN Number of Claims: 81
ECL Exemplary Claim: 1
DRWN 342 Drawing Page(s)
LN.CNT 4432
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention provides methods and systems to identify enzymes that act as enzyme catalyzed therapeutic activators and the enzymes identified by these methods. Also provided by this invention are compounds activated by the enzymes as well as compositions containing these compounds.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PRAI US 2000-219598P 20000720 (60) <--
PRAI US 2000-244953P 20001101 (60) <--
DETD . . . aziridinium ions. Functional groups that are unmasked or revealed include the conversion of vinyl halides to allyl halides as in **NB1011** (discussed infra).
DETD . . . tumor tissue allows for a positive therapeutic index to be achieved with ECTA compounds. Using this approach, the ECTA compound **NB1011** (See U.S. Pat. No. 6,245,750) targets the enzyme thymidylate synthase (TS) which is overexpressed in cancer cells. Cytotoxicity of **NB1011** is proportional to TS protein levels in model cell-based systems. TS inhibitors such as 5-fluorouridine have the reverse cytotoxicity profile. . .

L16 ANSWER 4 OF 10 USPATFULL on STN
AN 2003:160082 USPATFULL
TI Novel phosphoramidate compounds and methods of use
IN Shepard, H. Michael, Encinitas, CA, UNITED STATES
Vaino, Andrew Rein, San Diego, CA, UNITED STATES
Lehsten, Danielle M., San Diego, CA, UNITED STATES
PI US 2003109697 A1 20030612
AI US 2002-119927 A1 20020409 (10)
RLI Continuation-in-part of Ser. No. US 2001-782721, filed on 12 Feb 2001, PENDING Continuation of Ser. No. US 1999-235961, filed on 22 Jan 1999, GRANTED, Pat. No. US 6339151
PRAI US 1998-72264P 19980123 (60) <--
US 1998-76950P 19980305 (60) <--
US 1998-108634P 19981116 (60) <--
DT Utility
FS APPLICATION
LREP McCutchen, Doyle, Brown & Enersen LLP, Suite 1800, Three Embarcadero Center, San Francisco, CA, 94111
CLMN Number of Claims: 30
ECL Exemplary Claim: 1
DRWN 10 Drawing Page(s)
LN.CNT 3503
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention provides compounds, compositions and methods for treating cancer, infectious disease, an autoimmune disorder or an inflammatory condition. Therapeutic compounds useful in the methods of this invention are 5'-phosphoramidatyl, 1,5-substituted pyrimidine compounds, derivatives, analogs and pharmaceutically acceptable salts thereof

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PRAI US 1998-72264P 19980123 (60) <--
PRAI US 1998-76950P 19980305 (60) <--
PRAI US 1998-108634P 19981116 (60) <--
DRWD [0022] FIGS. 3A and 3B show detection of BVdUMP in H630R10 cells treated with **NB1011**. H630 R10 cells were treated with 100 μM **NB1011** for 5 days, then analyzed by LC/MS as described in Materials and Methods.
DRWD [0023] FIG. 4 demonstrates that **NB1011** does not irreversibly inactivate TS in vivo. The effect of **NB1011** on TS activity in intact cells is completely reversible. TS activity was measured in intact RKO cells by release of [.sup.3H].sub.2O from 5-[.sup.3H]deoxyuridine as described in Materials and Methods. **NB1011** was washed out of cells by replacing with fresh media, incubating for 60 minutes at 37 ° C., then repeating. . .
DRWD [0024] FIGS. 5A and 5B show that there are marked similarities between in vitro efficacy requirements for **NB1011** and anti-HER2. A), Data are taken from Tables 4, 5, and 8. B). Data from Shepard, et al. (1991). Vertical. . .
DRWD [0025] FIG. 6 shows that **NB1011** is highly active against Tomudex resistant cancers. Cytotoxicity vs. TDX.sup.R cell lines was measured in the alamarBlue assay, as described. . .
DRWD [0027] FIG. 8A shows that **NB1011** inhibits growth of 5-FU resistant colon cancer. Treatment of nude mice bearing H630R10 (5FU Resistant) human colon carcinoma. Tumor measurements. . .

DRWD [0028] FIG. 8B shows long term response to **NB1011**. Analysis of pooled data at Day 25. Statistical analysis is described in the Materials and Methods section below.

DRWD . . . shown in Table 2, below. Compounds are identified by structure and a numerical designation.

TABLE 2

##STR20##	
R.sub.1	##STR21##
##STR22##	**NB 1011**
##STR23##	NB 1012
##STR24##	NB 1013
--CF.sub.3	NB 1014
##STR25##	NB 1016
##STR26##	NB 1017
--.tbd.--SiMe.sub.3	NB 1018
--.tbd.--H	NB 1019

--.tbd.--C.sub.8H.sub.17. . .

DRWD . . . are sensitive to the compounds of this invention that require the activating enzyme to generate toxin in the infected cell. **NB1011** 1 is an example of such a compound, directed against TS expressed by mammalian and human cells as well as. . .

DETD 5-(2-Bromovinyl)-2'-deoxyuridine phenyl N-methoxy-L-alaninyl phosphoramidate (**NB1011**)

DETD . . . liters of dichloromethane and passed through 800 g of silica gel. The major portion of BVdU-PA, referred to herein as **NB1011**, was passed through the column during the loading and finally the elution of **NB1011** was completed by passing 5 liters of 5% methanol in dichloromethane. All fractions containing **NB1011** were combined and evaporated to an oil, the residue was dissolved in 4 liters of ethyl acetate and the mixture. . .

DETD [0315] Tomudex Inhibition of **NB1011** Cytotoxicity. MCF7-TDX were transferred to a 384 well assay plate at 500 cells in 25 μL complete medium per well. After 24 hours (day 0), 25 μL complete medium containing a combination of **NB1011** in doubling serial dilutions from 1 mM and tomudex at discrete concentrations (0,1,10,100,1000 nM) were added in duplicate. Drug exposure. . .

DETD . . . continuous exposure to stepwise increases in TDX concentrations up to 2.0 μM. A resistant subline was selected for resistance to **NB1011** by continuous exposure of the parental MCF7 TDX cell line to medium supplemented without TDX but with 50 μM **NB1011**, a concentration approximately 16 times higher than the IC.sub.50 for **NB1011** in the parental MCF7 TDX cell line. After a dramatic initial cell killing effect, resistant colonies emerged, and vigorously growing monolayers were formed. TS protein level and IC.sub.50 for 5-FU, TDX, and **NB1011** were determined for the resultant MCF7 TDX/1011 cell line as described in above by western blot and the alamarBlue cytotoxicity. . .

DETD [0317] Analysis of **NB1011** in TS-expressing, 5-FU resistant, H630-10 colon carcinoma xenografts in vivo. H630-10 colon cancer cells, selected for resistance to 5-FU in. . . (single-factor ANOVA) to assure uniformity in starting tumor volumes between treatment and control groups at the beginning of the experiment. **NB1011** was administered by intraperitoneal (I.P.) or intratumoral (IT) injection. The dosage of experimental agents tested were as follows: Group 1:. . . DMSO vehicle control solution (IP), Group 2: 5-FU (15 mg/kg+5 days IP=the MTD for 5-FU in this model), Group 3: **NB1011**=1.25

mg+5 days (IP), Group 4: **NB1011**=2.5 mg+5 days (IP), Group 5: **NB1011**=3.5 mg+5 days (IP), Group 6: DMSO control (IT), Group 7: **NB1011**=1.25 mg+5 days (IT), and Group 8: **NB1011**=2.5 mg+5 days (IT). These doses were based on independent dose-finding experiments conducted in our laboratory and were near the maximum-tolerated dose of **NB1011** for this specific age and strain of female athymic mice. To assure accurate dosing, drug doses were individualized based upon animal weights determined immediately prior to each injection. Treatment with control solution or **NB1011** was initiated 10 days status post xenograft inoculation at which time xenograft volumes measured 45-68 mm.sup.3. Differences in day 25. . .

DETD . . . components, it remained possible that the intracellular milieu could provide components that would result in TS inactivation following conversion of **NB1011** to the free nucleotide monophosphate inside the cell. This issue is addressed in more detail below.

DETD . . . casei TS leads to the prediction that the efficiency of enzymatic reaction within the cell would be too low for **NB1011** to be an effective therapeutic substrate, since it would have to compete with large amounts of endogenous dUMP. The discovery. . . that the human enzyme has a >6.4-fold improved efficiency of conversion of BVdUMP, is an important factor enabling utility of **NB1011**. The increased efficiency of BVdUMP utilization by the human enzyme as compared to the L. casei enzyme also establishes that. . .

DETD . . . purified rHuTS. Knowledge of the products of this reaction may be used to understand the final mechanism of action of **NB1011**. In addition, this information could be used to design novel chemotherapeutics, since the products of the TS-BVdUMP reaction could, themselves,. . .

DETD [0331] 4. **NB1011** is Converted to the Monophosphate in Tumor Cells

DETD [0332] **NB1011** is converted from the phosphoramidate to the monophosphate form in cells, as a prerequisite for binding to TS. To determine. . . BVdUMP (411 and 413 daltons). H630 R10 tumor cells (which express high levels of TS) were incubated with 100 FM **NB1011**. Extracts of treated cell lysates were prepared as described herein. Detection using mass spectroscopy, following an initial purification with liquid. . .

DETD Characterization of the Cytotoxic Activity of **NB1011**

DETD [0334] As an initial step in characterizing the biological activity of **NB1011**, a large series of normal and tumor cell types were tested in the alamarBlue assay for sensitivity to both **NB1011** and 5-fluorouracil.

DETD [0336] These data show that **NB1011** has met the primary design goal for TS ECTA compounds, i.e. increased potency on tumor cells vs. normal cell types. Overall, **NB1011** is about 2-fold more cytotoxic to tumor cells vs. normal cells, while 5-FU is 3-fold more toxic to normal cells than it is to tumor cells. The total benefit of **NB1011** is therefore (2)+(3)=6-fold improvement in therapeutic index for **NB1011** as compared with 5-FU. A critical tactic that allows for selection of chemotheraputics with a positive therapeutic index is screening. . .

DETD [0337] 2. **NB1011** Does Not Inactivate TS in Vivo

DETD [0338] The results described above indicate that BVdUMP, generated intracellularly from **NB1011**, is unlikely to inactivate TS during its transformation to product(s). However, the cell free system is different from the intracellular. . . is monitored (Carreras, C. W. and Santi, D. V. (1995) and Roberts (1966)). FIG. 4 shows that the presence of **NB1011** in cell culture media reduces the rate at which [.sup.3H].sub.2O is released from 5-[.sup.3H]dUMP. In order to determine whether this is the result of irreversible inhibition of TS, **NB1011**-treated cells were allowed to briefly recover in fresh culture media, then assayed for TS activity. Cells that have been allowed to recover in culture media lacking **NB1011** have the same level of TS activity as untreated cells. This result supports the proposal that **NB1011** does not irreversibly inactivate the TS enzyme following intracellular processing.

DETD [0339] An additional approach was taken to understanding whether **NB1011** might interfere with cell growth primarily by

inactivating TS. This approach is based upon thymidine rescue of TS-blocked cells. Cells. . . thus continue DNA synthesis. Other pathways for use of exogenous thymidine have also been described If an important mechanism for **NB1011** activity is via inhibition of endogenous TS, then the cytotoxicity should be relieved when thymidine is added to the cell. . . from these agents via thymidine supplementation. The normal colon epthelial cell, CCD18co, was used because of its measurable sensitivity to **NB1011**, 5FUdR and Tomudex. Experiments were carried out as described by (Patterson, et al. (1998)) with or without 10 μM thymidine,. . .

DETD [0340] 3. Relationship Between TS Level and **NB1011**-mediated Cytotoxicity on Tumor Cell Lines

DETD [0341] Confirmation that TS participates in **NB1011**-mediated cytotoxicity was established using several approaches: 1). The activity of **NB1011** was examined on normal colon cells vs. high TS expressing, 5FU-resistant, tumor cells; 2). transfection of TS into a tumor. . .

DETD [0342] In the initial analysis, of **NB1011** and 5FUdR-mediated cytotoxicity were compared on the CCD18co normal colon epithelial cell type and H630R.sup.10, 5FU-resistant colon tumor cell line. . .

DETD . . . has also been reported for doxorubicin (Smith, et al. (1985) and Smith, et al. (1990)). In contrast to 5FUdR, however, **NB1011** has more than an 11 -fold improved activity on drug-resistant H630R10 cells (IC.sub.50=216.7 μM) vs. normal colon epithelial cells (IC.sub.50 greater than 2500 μM). This result suggests that: 1). Activity of **NB1011** is more pronounced on high TS expressing tumor cells; and 2). A total improvement in therapeutic index of (18)+(11)=198-fold is. . .

DETD [0344] 4. Overexpression of TS in HT1080 Tumor Cells Enhances Their Sensitivity to **NB1011**

DETD [0345] Activation of **NB1011** requires several steps. These include cell penetration conversion to the nucleotide monophosphate, binding to TS, and subsequent toxic metabolism. The. . .

DETD . . . are particularly significant because they demonstrate, in a fairly uniform genetic background, that increasing TS levels predicts enhanced sensitivity to **NB1011**. In addition, the data also show that increasing TS levels predicts resistance to fluoropyrimidines, a result consistent with reports in. . .

DETD [0347] 5. Inhibitors of **NB1011**-mediated Cytotoxicity

DETD [0348] Tomudex is a chemotherapeutic that acts primarily via inhibition of TS. If **NB1011** exerts cytotoxicity via the TS enzyme, then inhibition of TS with Tomudex should decrease **NB1011**-mediated cytotoxicity. To test this hypothesis directly, Tomudex-resistant MCF7 cells, which overexpress TS 11-fold compared to the parental MCF7 cell line, were exposed to **NB1011** in the presence of increasing concentrations of TDX. Cells were plated and exposed to indicated concentrations of compound(s) as described. . .

DETD . . . The data show that blockade of TS using the specific inhibitor Tomudex, results in up to about 25-fold inhibition of **NB1011** -mediated cytotoxicity. These results support the concept that activity of **NB1011** results from its metabolism by TS.

DETD [0350] To further characterize the intracellular metabolism of **NB1011**, combination experiments with leucovorin (LV; 5-formyltetrahydrofolate) were performed. This experiment was initiated because we had observed that THF stimulates production. . . reaction of BVdUMP and rHuTS. It was hypothesized that if the fluorescent products are related to the cytotoxic effects of **NB1011**, then enhancing intracellular levels of THF by providing LV in the culture media would also enhance **NB1011**-mediated cytotoxic effects. Surprisingly, in the presence of 3 μM LV, **NB1011** activity on the H630R10 cell line was diminished by more than 90%, compared to **NB1011** alone, as determined in the alamarBlue assay. The fact that **NB1011** activity is abolished by LV, which supplements intracellular reduced folate pools, suggests that **NB1011** may work in part by diminishing these pools. Alternatively, LV (or a metabolite) could directly impact the metabolism of BVdUMP. . .

DETD . . . LV, MTX and TDX, and further, that this effect is more pronounced in the presence of cofactor (THF), suggests that **NB1011** activity may be modulated by other chemotherapeutics.

Importantly, rescue of **NB1011**-treated cells is feasible by providing LV, similar to the LV rescue from MTX. In the case of MLX, LV rescue. . . intracellular thymidine or purine nucleotide pools by distinct mechanisms may give additive or synergistic anti-cellular effects when used together with **NB1011**. Examples of such compounds (Dorr and Von Hoff (1994)),include 6-mercaptopurine, thioguanine and 2i-deoxycoformycin, all of which interfere with purine metabolism.. . . blocks pyrimidine biosynthesis, and so could lower intracellular thymidine levels in a cell by a mechanism distinct from that of **NB 1011**.

DETD [0358] 2. **NB1011** is Active Against 5FU and Tomudex-resistant Colon and Breast Tumor Cell Lines

DETD [0359] Because **NB1011** has promising anticancer activity, it is important to compare it with other chemotherapeutics with respect to safety. The utility of **NB1011** in the treatment of cancer is further strengthened when it is compared with Tomudex, a chemotherapeutic which, like 5FU, is. . .

DETD [0360] The results (FIG. 10) show that while **NB1011** is more than 10-fold less toxic than TDX vs. normal cells (CCD18co), it is more than 30-fold more potent than. . . The low level of toxicity vs. normal cells and the high activity vs. TDX.sup.R tumor cells supports the application of **NB1011** to drug resistant cancers that overexpress TS.

DETD [0361] 3. **NB1011** is More Dependent Upon TS Protein Levels than TS Activity as Measured by Tritium Release from dUMP-.sup.3H

DETD . . . the data presented in Table 7 indicates that there is a closer relationship between TS protein level and sensitivity to **NB1011** than between TS activity (tritium release from .sup.3H-dUMP) and **NB1011** sensitivity. In each set of matched parental and drug-resistant tumor cell types, the drug-resistant derivatives, each with more TS protein than the parent, also have an increased sensitivity to **NB1011**. However, when the same comparison is done with respect to TS activity, the parental cell lines often have comparable, or greater, TS activity and are less sensitive to **NB1011** -mediated cytotoxicity.

DETD [0367] The results shown above suggest that TS ECTA therapy, at least with **NB1011**, will be most effective when used in patients whose cancers overexpress TS at least four-fold.

DETD [0371] The most important diseases for new compounds that target TS are the gastrointestinal cancers. To study the activity of **NB1011** in an in vivo model, H630R10, 5FU-resistant human colon cancer cells, were grown subcutaneously to an average tumor size of 50 mm.sup.3 in nude mice. The mice were then treated, with excipient (DMSO, 5FU or **NB1011**).

DETD [0372] Doses of 3.5 mg, 2.5 mg, and 1.25 mg of **NB1011** were administered daily for 5 days, either peritumorally or intraperitoneally to tumor-bearing mice. FIG. 8A shows the initial block in tumor growth induced by treatment for 5 days with **NB1011**, as compared to excipient or 5FU treated animals. Although no statistically significant dose response relationship is evident among the **NB1011** groups, there is a significant difference between the **NB1011** groups vs. either the 5FU or excipient controls, starting with Day 6. This difference is maintained (FIG. 9B) until the. . .

DETD [0374]

TABLE 5

Cytotoxicity of **NB1011** vs. 5FU on Normal and Tumor Cell Strains

IC.sub.50 (μM)			IC.sub.50 (μM)	
Normal Cells	NB101.1	5FU	Tumor Cells	NB101.1 5FU
CCD1800 (Colon)	562. . .	0.2		
			MCIxc (Brain)	61. 1.2
			Average	288

5.3

	NB101.1	5FU
Therapeutic index (N/T)	1.95	0.30

Cells were analyzed for response to either **NB1011** or 5FU in the alamarBlue assay (Methods). All assays were performed at least three times. The standard deviation is less. . .
DETD [0375]
TABLE 6

NB1011 cytotoxicity on cell lines engineered to express HuTS.

Cell Line	TS Level (%)*	IC.sub.50 **NB1011** (μM)	FUDR (μM)	5-FU (μM)	TDX (μM)
.sup. C/HT1080	100	320	<0.1	1.0	3.6
TSL/HT1080	409	196	2.2	1.7	24

TSL/HT1080. . .
DETD [0376]
TABLE 7

Tomudex Inhibits **NB1011** Mediated Cytotoxicity

[Tomudex] (nM)	0 nM	1 nM	10 nM	100 nM	1000 nM
NB1011IC.sub.50 (μM)	5.7	25.5	87.7	140.3	103.0
Fold Protection	1. . .				

DETD [0378]
TABLE 9

NB1011 activity is more associated with TS protein than with tritium release

Cell Line	Drug Selection	TS Protein	Tritium Release	**NB1011**-IC.sub.50
H630	None	288	3206	414
Colon cancer	5FU	2350	1840	65
	TDX	671	3980	2.3
RKO	None. . .			

DETD [0379]
TABLE 10

MDF7 TDX cells selected for resistance to **NB1011** are more sensitive to 5-Fluorouracil and Tomudex

	IC.sub.50 (micromolar)* 5-FU	Tomudex	**NB1011**	Relative TS Protein Level
MCF7	10-	.026-	291-	1X-
MCF7 TDX	32	>10	2	11X
MCF7 TDX/1011	2	.041	240	4X

*= as determined by the alamarBlue assay described in Materials and Methods
TDX = Tomudex;
1011 = **NB 1011**
DETD [0387] 384-well screening studies. To identify drugs which potentially synergize with **NB1011**, combination cytotoxicity experiments were performed with **NB1011** and each of 10 antitumor agents from several different mechanistic classes using MCF7TDX and H630R10 tumor cells. Results from these. . . synergy, .about.1 indicates additivity, and >1 indicates antagonism (Pegram, M. D. et al. (1999)).
TABLE 11

Drugs screened for interaction with **NB1011**

Drug	Class	Combination Index ± s.e.m. MCF7 TDX	H630R10
Irinotecan	Inhibition of topoisomerase I	1.36 ± 0.38	1.26 ± 0.20
topotecan		2.45 ±. . .	

DETD [0388] Two of the ten agents screened, vinblastine and doxorubicin, showed potential synergy (CI≤1.1) with **NB1011** in MCF7TDX and H630R10 cell. Two of the remaining 8 agents, irinotecan and taxol showed an additive or antagonistic interaction (CI=1-1.4) with **NB1011**, while all the other agents showed antagonism (CI>1.5). The most antagonistic interaction was observed with 5-Fluorouracil which gave CI=3.19 in. . . may modulate the activity of nucleoside based drugs. To analyze whether any of these drugs would enhance the activity of **NB1011** specifically in tumor cells, two normal cell types, Det551 and CCD18co, were included in the assays. Results of these experiments are shown in Table 12.

TABLE 12

Average combination index (CI) values for drugs tested in combination with **NB1011** in tumor and normal cells

Drug	Drug Dose (μM)	Cell Line	CI	±SEM	P value	Molar Ratio.sup.a	**NB1011** Dose (μM)
Dipyridamole	5.5-75.	H630R10 . . 0.1-1.3	0.75 Inter-action.sup.b	0.11 Ant	0.052	2	11-150
Doxorubicin	0.039-0.5	H630R10	1.39 Ant	0.13	0.012	300	117-150
	0.001-0.025	MCF7TDX	1.96 Ant	0.25	0.004	600	1.9-15

.sup.aMolar ratio of **NB1011**:Drug.
.sup.bSyn = synergy,
Ant = antagonism,
Add = additivity.

DETD . . . respectively). Oxaliplatin had an antagonistic interaction in the tumor cells (CI=1.78 and 2.24, respectively). Since both oxaliplatin and doxorubicin antagonized **NB1011** in the tumor cells, they were not tested in the normal cell assays. Consistent with the initial screening data, vinblastine synergized with **NB1011** in H630R10 cells (CI=0.63), however it antagonized **NB1011** in MCF7TDX cells (CI=1.44). Furthermore, in Det551 and CCD18co normal cells, vinblastine interacted synergistically with **NB1011** to a similar extent as in H630R10 cells (CI=0.54 and 0.65, respectively). This lack of selectivity in the potentiation of **NB1011** by vinblastine would most likely limit the use of this combination in the clinic. The nucleoside transport inhibitor, dipyridamole, synergized with **NB1011** in the tumor cells (CI=0.75 and 0.51), but failed to synergize with **NB1011** in the normal cells (CI=1.17 and 1.30). Similarly, NBMPR, another NT inhibitor, showed synergy with NB31011 in the tumor cells. . . of the 13 agents tested, DP and NBMPR, which are both inhibitors of equilibrative nucleoside transport, potentiate the activity of **NB1011**. This enhancement of **NB1011** activity by DP and NBMPR appears specific for the tumor cells tested, since no synergy was observed for these combinations. . .

DETD [0392] Anti-TNF antibody used in these experiments was as described by Marinova-Mutafchieva, L. et al. (2000). **NB1011** was administered daily by intraperitoneal administration at 2.5 mg total dose per day. Anti-TNF antibody was compared with **NB1011** because, at present, antiTNF antibody is the optimal single agent for treatment of collagen induced arthritis (Marinova-Mutafchieva, L. et al.. . .

DETD . . . significant clinical score for disease progression was achieved

(between 2.5 and 3.5). Mice were then treated with control saline injections, **NB1011**, or with anti-TNF antibody as a positive control. The results showed that the **NB1011**-treated group exhibited significant disease suppression ($p<0.05$), similar to the anti-TNF control, when compared with the saline-treated control group. There was no significant difference between the **NB1011** and anti-TNF groups with regard to clinical score. Paw swelling is an alternative measure of CIA disease severity. When paw. . . was used as a criteria for disease suppression, comparable results were observed. In this second measure of efficacy, both the **NB1011** and anti-TNF groups demonstrated significant disease suppression as compared to the saline-treated control group ($p<0.05$). Again, there was no significant difference between the **NB1011** and anti-TNF groups, although suppression of swelling may have been less dramatic with **NB1011**. A further significant outcome of this work is that by comparison with earlier reported work, **NB1011** appears to have activity superior to anti-angiogenesis agents, an anti-CD4 immunosuppressive agent, and cannabidiol, a third experimental agent currently being. . .

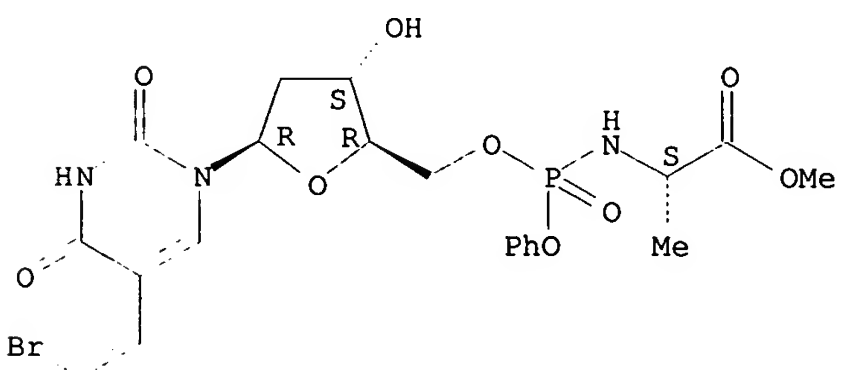
IT 142629-80-9P 321982-16-5P 321982-20-1P 321982-22-3P 321982-24-5P
321982-26-7P 321982-28-9P 321982-30-3P 321982-34-7P 322454-13-7P
322454-48-8P **322454-65-9P** 436097-54-0P 535958-45-3P
535958-46-4P 535958-47-5P 535958-48-6P 535958-49-7P 535958-50-0P
535958-51-1P 535958-52-2P 535958-53-3P 535958-54-4P 535958-55-5P
535958-57-7P 535958-58-8P 535958-59-9P 535958-60-2P 535958-61-3P
535958-62-4P 535958-63-5P 535958-64-6P
(preparation cytotoxicity antitumor and antiinflammatory activities of nucleoside phosphoramidates)

IT **322454-65-9P**
(preparation cytotoxicity antitumor and antiinflammatory activities of nucleoside phosphoramidates)

RN 322454-65-9 USPATFULL

CN L-Alanine, N-[5-(2-bromoethenyl)-2'-deoxy-P-phenyl-5'-uridylyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



L16 ANSWER 5 OF 10 USPATFULL on STN
AN 2002:273391 USPATFULL
TI Methods to treat autoimmune and inflammatory conditions
IN Shepard, H. Michael, Encinitas, CA, UNITED STATES
PI US 2002151519 A1 20021017
AI US 2002-51320 A1 20020118 (10)
PRAI US 2001-262849P 20010119 (60)
DT Utility
FS APPLICATION
LREP McCutchen, Doyle, Brown & Enersen LLP, Suite 1800, Three Embarcadero Center, San Francisco, CA, 94111
CLMN Number of Claims: 22
ECL Exemplary Claim: 1
DRWN 3 Drawing Page(s)
LN.CNT 1850
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention provides methods for treating inflammatory or autoimmune

diseases by contacting the affected cell or tissue with a therapeutic compound as described herein. Such pathologies include, but are not limited to rheumatoid arthritis, systemic lupus erythmatosus, psoriatic arthritis, reactive arthritis, Crohn's disease, ulcerative colitis and scleroderma. Therapeutic compounds useful in the methods of this invention are selected from the group consisting of a 1,5-substituted pyrimidine derivative or analog and substituted furano-pyrimidone analog.

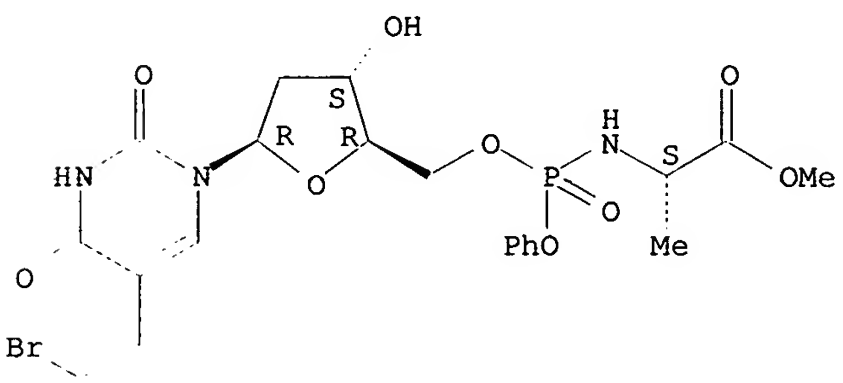
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PRAI US 2001-262849P 20010119 (60) <--
DRWD [0010] FIG. 1 shows clinical scoring of animals with collagen-induced arthritis using **NB 1011**, a 5'-phosphoramidatyl deoxyuridine derivate and controls.
DETD . . . shown in Table I, below. Compounds are identified by structure and a numerical designation. ##STR19##

R	##STR20##	Y.dbd.H
##STR21## NB 1015 (BVdU)	**NB 1011**	
##STR22##	NB 1012	--
##STR23##	NB 1013	NB 1020
--CF.sub.3	NB 1014	NB 1027
##STR24##	NB 1016. . .	

DETD [0207] 5-(2-Bromovinyl)-2'-deoxyuridine phenyl N-methoxy-L-alaninyl phosphoramidate (**NB1011**)
DETD . . . liters of dichloromethane and passed through 800 g of silica gel. The major portion of BVdU-PA, referred to herein as **NB1011**, was passed through the column during the loading and finally the elution of **NB1011** was completed by passing 5 liters of 5% methanol in dichloromethane. All fractions containing **NB1011** were combined and evaporated to an oil, the residue was dissolved in 4 liters of ethyl acetate and the mixture. . .
DETD Treatment of Animals with Anti-TNF or **NB 1011**
DETD [0225] Anti-TNF antibody was used in these experiments was as described by Marinova-Mutafchieva, L. et al. (2000). **NB1011** was administered daily by intraperitoneal administration at 2.5 mg total dose per day. Anti-TNF antibody was compared with **NB1011** because, at present, antiTNF antibody is the optimal single agent for treatment of collagen induced arthritis (Marinova-Mutafchieva, L. et al.. . .
DETD . . . progression was achieved (between 2.5 and 3.5, see FIG. 1 and Methods). Mice were then treated with control saline injections, **NB1011**, or with anti-TNF antibody as a positive control. The results (FIG. 1) show that the **NB1011**-treated group exhibited significant disease suppression ($p<0.05$), similar to the anti-TNF control, when compared with the saline-treated control group. There was no significant difference between the **NB1011** and anti-TNF groups with regard to clinical score. Paw swelling is an alternative measure of CIA disease severity. When paw. . . as a criteria for disease suppression, comparable results were observed (FIG. 2). In this second measure of efficacy, both the **NB1011** and anti-TNF groups demonstrated significant disease suppression as compared to the saline-treated control group ($p<0.05$). Again, there was no significant difference between the **NB1011** and anti-TNF groups, although suppression of swelling may have been less dramatic with **NB1011**. A further significant outcome of this work is that by comparison with earlier reported work, **NB1011** appears to have activity superior to anti-angiogenesis agents, an anti-CD4 immunosuppressive agent, and cannabidiol, a third experimental agent currently being. . .

IT **322454-65-9P**
(pyrimidine derivs. and furanopyrimidone derivs.,for treatment of autoimmune and inflammatory conditions)
IT **322454-65-9P**
(pyrimidine derivs. and furanopyrimidone derivs.,for treatment of autoimmune and inflammatory conditions)
RN 322454-65-9 USPATFULL
CN L-Alanine, N-[5-(2-bromoethenyl)-2'-deoxy-P-phenyl-5'-uridylyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



L16 ANSWER 6 OF 10 USPATFULL on STN
AN 2002:266296 USPATFULL
TI Synergistic ECTA compositions
IN Shepard, H. Michael, Encinitas, CA, UNITED STATES
Boyer, Christopher, San Diego, CA, UNITED STATES
PI US 2002147175 A1 20021010
AI US 2001-990799 A1 20011116 (9)
PRAI US 2000-249722P 20001116 (60) <--
DT Utility
FS APPLICATION
LREP Antoinette F. Konski, McCutchen Doyle Brown & Enersen LLP, Three Embarcadero Center, Suite 1800, San Francisco, CA, 94111
CLMN Number of Claims: 52
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 2274
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention provides compositions containing an effective amount of a novel substrate compound that selectively inhibit the proliferation of hyperproliferative cells, for example, pathological cells that endogenously overexpress a target enzyme that confers resistance to biologic and chemotherapeutic agents and an effective amount of a nucleoside transport antagonistic agents. Further provided by this invention is a method for treating a subject by delivering to the subject the composition as described herein. The compositions of this invention may be used alone or in combination with other chemotherapeutics or alternative anti-cancer therapies such as radiation.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PRAI US 2000-249722P 20001116 (60) <--
SUMM . . . takes advantage of the overexpression of thymidylate synthase (TS) in many tumor cells. One TS ECTA compound, (E)-5-(2-bromovinyl)-2'-deoxy-5'-uridyl phenyl L-alaninylphosphoramidate ("**NB 1011**") is a nucleotide analog phosphoramidate, which upon entry into cells is converted to bromovinyldeoxyuridine monophosphate (BVdUMP) (Lackey, D. B. et. . . during an enzymatic reaction catalyzed by TS, BVdUMP is converted into proposed cytotoxic product(s) (Lackey, D. B. et al. (2000)). **NB1011** is preferentially cytotoxic to tumor cells displaying elevated TS levels as compared to normal cells which have lower levels of TS. Furthermore, **NB1011** was shown to have antitumor activity in colon and breast carcinoma xenografts in athymic

mice (Lackey, D. B. et al.. . .
SUMM . . . especially applies to the lack of synergistic toxicity on normal cells. The results reported herein also supports the theory that **NB1011** is a nucleotide substrate of thymidylate synthase, as opposed to the classical inhibitors of TS function now in clinical use.
SUMM . . . are shown in Table I, below. Compounds are identified by structure and a numerical designation.

##STR19##

R ##STR20## Y.dbd.H

##STR21## **NB 1011**
NB 1015 (BVdU)

##STR22## NB 1012 --

##STR23## NB 1013 NB 1020

--CF.sub.3 NB 1014 NB 1027

##STR24## NB 1016. . .
DETD [0210] 5-(2-Bromovinyl)-2'-deoxyuridine phenyl N-methoxy-L-alaninyl phosphoramidate (**NB1011**)
DETD . . . liters of dichloromethane and passed through 800 g of silica gel. The major portion of BVdU-PA, referred to herein as **NB1011**, was passed through the column during the loading and finally the elution of **NB1011** was completed by passing 5 liters of 5% methanol in dichloromethane. All fractions containing **NB 1011** were combined and evaporated to an oil, the residue was dissolved in 4 liters of ethyl acetate and the mixture. . .
DETD [0242] To identify drugs which potentially synergize with **NB1011**, combination cytotoxicity experiments were performed with **NB 1011** and each of 10 antitumor agents from several different mechanistic classes using MCF7TDX and H630R10 tumor cells. Results from these. . . synergy, .about.1 indicates additivity, and >1 indicates antagonism (Pegram, M. D. et al. (1999)).
TABLE 2

Drugs screened for interaction with **NB1011**

		Combination Index ± s.e.m.	
Drug	Class	MCF7TDX	H630R10
Irinotecan	Inhibition of topoisomerase I	1.36 ± 0.38	1.26 ± 0.20
Topotecan	2.45 ± 0.85. . .		

DETD [0244] Two of the ten agents screened, vinblastine and doxorubicin, showed potential synergy (CI≤1.1) with **NB1011** in MCF7TDX and H630R10 cell. Two of the remaining 8 agents, irinotecan and taxol showed an additive or antagonistic interaction (CI=1-1.4) with **NB1011**, while all the other agents showed antagonism (CI>1.5). The most antagonistic interaction was observed with 5-Fluorouracil which gave CI=3.19 in. . .
DETD . . . may modulate the activity of nucleoside based drugs. To analyze whether any of these drugs would enhance the activity of **NB1011** specifically in tumor cells, two normal cell types, Det551 and CCD18co, were included in the assays. Results of these experiments are shown in Table 3.
TABLE 3

Average combination index (CI) values for drugs tested in combination with **NB1011** in tumor and normal cells

Drug	Dose Cell	Inter-Line	CI	± SEM	P value	Molar Ratio.sup.a	**NB1011** Dose (μM)

(μM) action.sup.b

Dipyridamole	H630R10	0.75	0.11	0.052	2	11-150
5.5-75. . . 0.1-1.3		Ant				
Doxorubicin	H630R10	1.39	0.13	0.012	300	117-150
0.039-0.5	Ant					
	MCF7TDX	1.96	0.25	0.004	600	1.9-15
0.001-0.025	Ant					

.sup.aMolar ratio of **NB1011**:Drug. .sup.bSyn = synergy, Ant = antagonism, Add = additivity.

DETD . . . respectively). Oxaliplatin had an antagonistic interaction in the tumor cells (CI=1.78 and 2.24, respectively). Since both oxaliplatin and doxorubicin antagonized **NB 1011** in the tumor cells, they were not tested in the normal cell assays. Consistent with the initial screening data, vinblastine synergized with **NB1011** in H630R10 cells (CI=0.63), however it antagonized **NB1011** in MCF7TDX cells (CI=1.44). Furthermore, in Det551 and CCD18co normal cells, vinblastine interacted synergistically with **NB 1011** to a similar extent as in H630R10 cells (CI=0.54 and 0.65, respectively). This lack of selectivity in the potentiation of **NB1011** by vinblastine would most likely limit the use of this combination in the clinic. The nucleoside transport inhibitor, dipyridamole, synergized with **NB1011** in the tumor cells (CI=0.75 and 0.51), but failed to synergize with **NB1011** in the normal cells (CI=1.17 and 1.30). Similarly, NBMPR, another NT inhibitor, showed synergy with **NB1011** in the tumor cells (CI=0.35 and 0.57), but produced no synergy in the normal cells (CI=1.43 and 3.93). Taken together. . . of the 13 agents tested, DP and NBMPR, which are both inhibitors of equilibrative nucleoside transport, potentiate the activity of **NB1011**. This enhancement of **NB1011** activity by DP and NBMPR appears specific for the tumor cells tested, since no synergy was observed for these combinations. . .

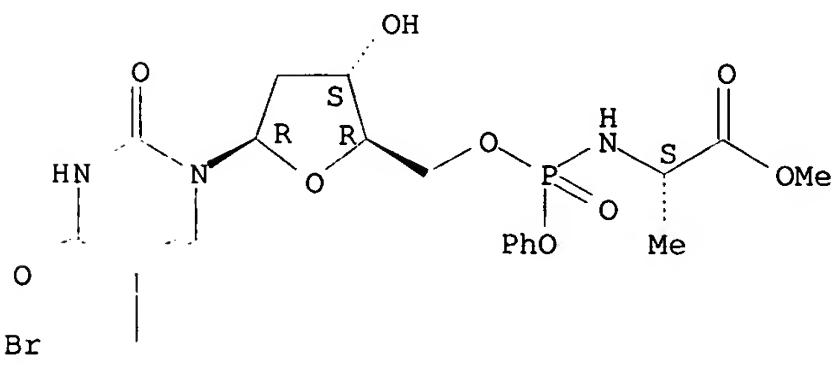
IT 157085-09-1P 321982-16-5P 321982-20-1P 321982-22-3P 321982-24-5P
321982-26-7P 321982-28-9P 321982-30-3P 321982-34-7P 322454-13-7P
322454-17-1P **322454-65-9P**
(preparation of synergistic enzyme catalyzed therapeutic activation nucleosides as antitumor agents)

IT **322454-65-9P**
(preparation of synergistic enzyme catalyzed therapeutic activation nucleosides as antitumor agents)

RN 322454-65-9 USPATFULL

CN L-Alanine, N-[5-(2-bromoethenyl)-2'-deoxy-P-phenyl-5'-uridylyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

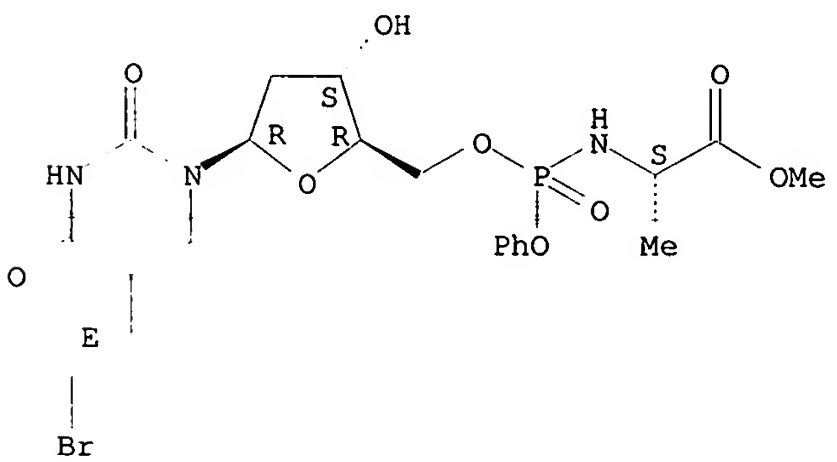


L16 ANSWER 7 OF 10 USPATFULL on STN
AN 2002:9933 USPATFULL
TI Enzyme catalyzed therapeutic agents
IN Shepard, H. Michael, Rancho Santa Fe, CA, United States
Groziak, Michael P., Palo Alto, CA, United States
PA NewBiotics, Inc., San Diego, CA, United States (U.S. corporation)
PI US 6339151 B1 20020115

AI US 1999-235961 19990122 (9) <--
PRAI US 1998-108634P 19981116 (60) <--
US 1998-76950P 19980305 (60) <--
US 1998-72264P 19980123 (60) <--
DT Utility
FS GRANTED
EXNAM Primary Examiner: Fonda, Kathleen Kahler; Assistant Examiner: Crane, L. E.
LREP Konski, Antoinette F., McCutchen, Brown, Doyle & Enersen LLP
CLMN Number of Claims: 9
ECL Exemplary Claim: 1,2,3,4
DRWN 8 Drawing Figure(s); 8 Drawing Page(s)
LN.CNT 3289
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention provides a method for identifying potential therapeutic agents by contacting a target cell with a candidate therapeutic agent which is a selective substrate for an endogenous, intracellular enzyme in the cell which is enhanced in its expression as a result of selection by biologic or chemotherapy. This invention also provides methods and examples of molecules for selectively killing a pathological cell by contacting the cell with a prodrug that is a selective substrate for an endogenous, intracellular enzyme. The prodrug is subsequently converted to a cellular toxin. Further provided by this invention is a method for treating a pathology characterized by pathological, hyperproliferative cells in a subject by administering to the subject a prodrug that is a selective substrate for an endogenous, overexpressed, intracellular enzyme, and converted by the enzyme to a cellular toxin in the hyperproliferative cell.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AI US 1999-235961 19990122 (9) <--
PRAI US 1998-108634P 19981116 (60) <--
PRAI US 1998-76950P 19980305 (60) <--
PRAI US 1998-72264P 19980123 (60) <--
IT **232925-18-7P** 232925-20-1P
(method for drug screening and enzyme-activated phosphoryl or phosphoramidate prodrugs and their synthesis and use in inhibition of cell proliferation)
IT **232925-18-7P**
(method for drug screening and enzyme-activated phosphoryl or phosphoramidate prodrugs and their synthesis and use in inhibition of cell proliferation)
RN 232925-18-7 USPATFULL
CN L-Alanine, N-[5-[(1E)-2-bromoethenyl]-2'-deoxy-P-phenyl-5'-uridylyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

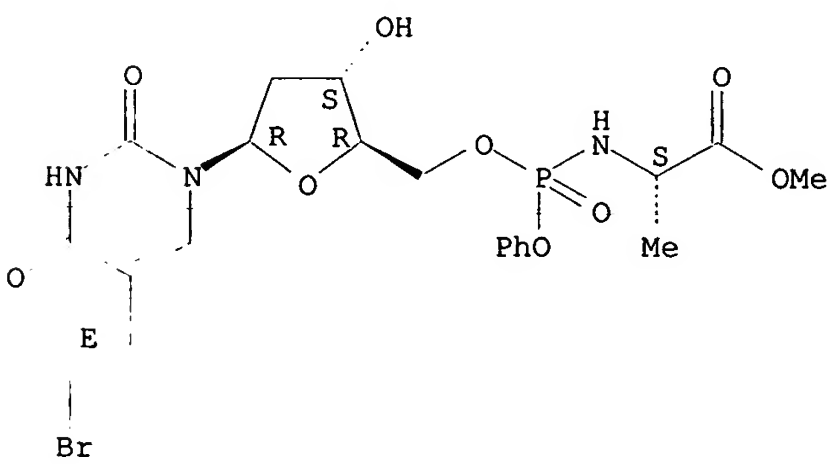


L16 ANSWER 8 OF 10 USPATFULL on STN
AN 2001:188806 USPATFULL
TI Enzyme catalyzed therapeutic agents
IN Shepard, H. Michael, Rancho Santa Fe, CA, United States

Groziak, Michael P., Palo Alto, CA, United States
PI US 2001034440 A1 20011025
AI US 2001-782721 A1 20010212 (9)
RLI Continuation of Ser. No. US 1999-235961, filed on 22 Jan 1999, PENDING
PRAI US 1998-72264P 19980123 (60) <--
US 1998-76950P 19980305 (60) <--
US 1998-108634P 19981116 (60) <--
DT Utility
FS APPLICATION
LREP BAKER & MCKENZIE, 660 HANSEN WAY, PALO ALTO, CA, 94304
CLMN Number of Claims: 55
ECL Exemplary Claim: 1
DRWN 8 Drawing Page(s)
LN.CNT 2939
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention provides a method for identifying potential therapeutic agents by contacting a target cell with a candidate therapeutic agent which is a selective substrate for an endogenous, intracellular enzyme in the cell which is enhanced in its expression as a result of selection by biologic or chemotherapy. This invention also provides methods and examples of molecules for selectively killing a pathological cell by contacting the cell with a prodrug that is a selective substrate for an endogenous, intracellular enzyme. The prodrug is subsequently converted to a cellular toxin. Further provided by this invention is a method for treating a pathology characterized by pathological, hyperproliferative cells in a subject by administering to the subject a prodrug that is a selective substrate for an endogenous, overexpressed, intracellular enzyme, and converted by the enzyme to a cellular toxin in the hyperproliferative cell.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PRAI US 1998-72264P 19980123 (60) <--
PRAI US 1998-76950P 19980305 (60) <--
PRAI US 1998-108634P 19981116 (60) <--
IT **232925-18-7P** 232925-20-1P
(method for drug screening and enzyme-activated phosphoryl or phosphoramidate prodrugs and their synthesis and use in inhibition of cell proliferation)
IT **232925-18-7P**
(method for drug screening and enzyme-activated phosphoryl or phosphoramidate prodrugs and their synthesis and use in inhibition of cell proliferation)
RN 232925-18-7 USPATFULL
CN L-Alanine, N-[5-[(1E)-2-bromoethenyl]-2'-deoxy-P-phenyl-5'-uridylyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

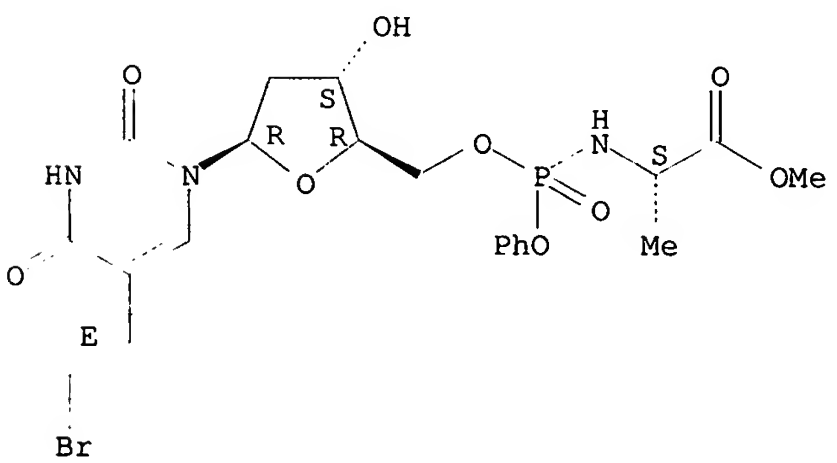


L16 ANSWER 9 OF 10 USPATFULL on STN
AN 2001:86452 USPATFULL
TI Enzyme catalyzed therapeutic agents
IN Shepard, H. Michael, Rancho Santa Fe, CA, United States

PA NewBiotics, Inc., San Diego, CA, United States (U.S. corporation)
PI US 6245750 B1 20010612
AI US 1999-235809 19990122 (9) <--
PRAI US 1998-72264P 19980123 (60) <--
DT Utility
FS GRANTED
EXNAM Primary Examiner: Geist, Gary; Assistant Examiner: Crane, L. E.
LREP Konski, Antoinette F.Baker & McKenzie
CLMN Number of Claims: 7
ECL Exemplary Claim: 1
DRWN 8 Drawing Figure(s); 8 Drawing Page(s)
LN.CNT 3298
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention provides a method for identifying potential therapeutic agents by contacting a target cell with a candidate therapeutic agent which is a selective substrate for an endogenous, intracellular enzyme in the cell which is enhanced in its expression as a result of selection by biologic or chemotherapy. This invention also provides methods and examples of molecules for selectively killing a pathological cell by contacting the cell with a prodrug that is a selective substrate for an endogenous, intracellular enzyme. The prodrug is subsequently converted to a cellular toxin. Further provided by this invention is a method for treating a pathology characterized by pathological, hyperproliferative cells in a subject by administering to the subject a prodrug that is a selective substrate for an endogenous, overexpressed, intracellular enzyme, and converted by the enzyme to a cellular toxin in the hyperproliferative cell.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AI US 1999-235809 19990122 (9) <--
PRAI US 1998-72264P 19980123 (60) <--
IT **232925-18-7P** 232925-20-1P
(method for drug screening and enzyme-activated phosphoryl or phosphoramidate prodrugs and their synthesis and use in inhibition of cell proliferation)
IT **232925-18-7P**
(method for drug screening and enzyme-activated phosphoryl or phosphoramidate prodrugs and their synthesis and use in inhibition of cell proliferation)
RN 232925-18-7 USPATFULL
CN L-Alanine, N-[5-[(1E)-2-bromoethenyl]-2'-deoxy-P-phenyl-5'-uridylyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

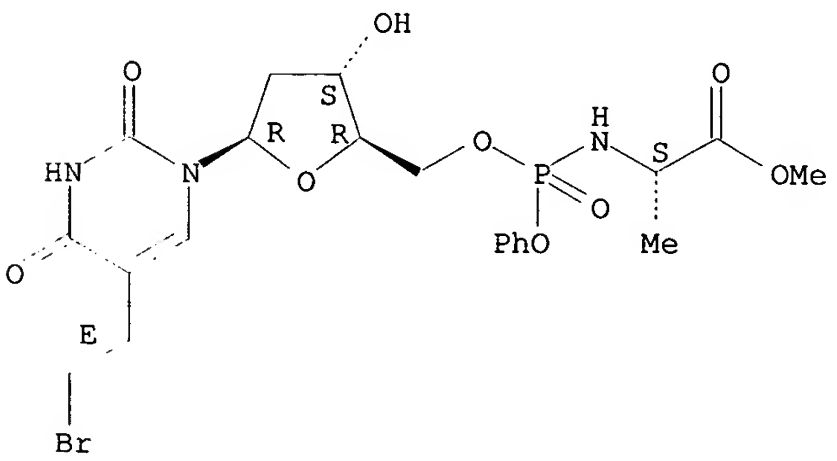


L16 ANSWER 10 OF 10 USPATFULL on STN
AN 2000:126824 USPATFULL
TI Air pad
IN Bondie, Philip, Saline, MI, United States
Gallmeyer, William, Holland, MI, United States
Bondie, Judith, Saline, MI, United States
Limperis, Thomas, Tecumseh, MI, United States

PA AirSports Technology, L.L.C., Saline, MI, United States (U.S. corporation)
PI US 6122785 20000926 <--
AI US 1998-108634 19980701 (9) <--
DT Utility
FS Granted
EXNAM Primary Examiner: Melius, Terry Lee; Assistant Examiner: Conley, Fredrick
LREP Harness, Dickey & Pierce, P.L.C.
CLMN Number of Claims: 5
ECL Exemplary Claim: 1
DRWN 13 Drawing Figure(s); 8 Drawing Page(s)
LN.CNT 326
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB An air pad having a plurality of foam filled air chambers interconnected by at least one air passage connecting at least two of the air chambers to one another. The air passages are also filled with foam whereby the flow of air from one air chamber to another due to impact is restricted. The pad is manufactured by radio frequency welding of two layers of plastic film to one another about a foam body to join the plastic film in the area surrounding each of the air chambers.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 6122785 20000926 <--
AI US 1998-108634 19980701 (9) <--
IT **232925-18-7P** 232925-20-1P
(method for drug screening and enzyme-activated phosphoryl or phosphoramidate prodrugs and their synthesis and use in inhibition of cell proliferation)
IT **232925-18-7P**
(method for drug screening and enzyme-activated phosphoryl or phosphoramidate prodrugs and their synthesis and use in inhibition of cell proliferation)
RN 232925-18-7 USPATFULL
CN L-Alanine, N-[5-[(1E)-2-bromoethenyl]-2'-deoxy-P-phenyl-5'-uridylyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



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